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Relieve bursitis pain

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Frankel and Strider[1] report: "Intravenous Priscoline gave excellent to good results in over 90% of our cases."

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"We can especially recommend its use in cases where X-ray therapy or local injection of hydrocortisone has failed."

1. Frankel, C. J., and Strider, D. V.: Presented at Meeting of American Academy of Orthopaedic Surgeons, New York, N. Y., Feb. 3, 1958.

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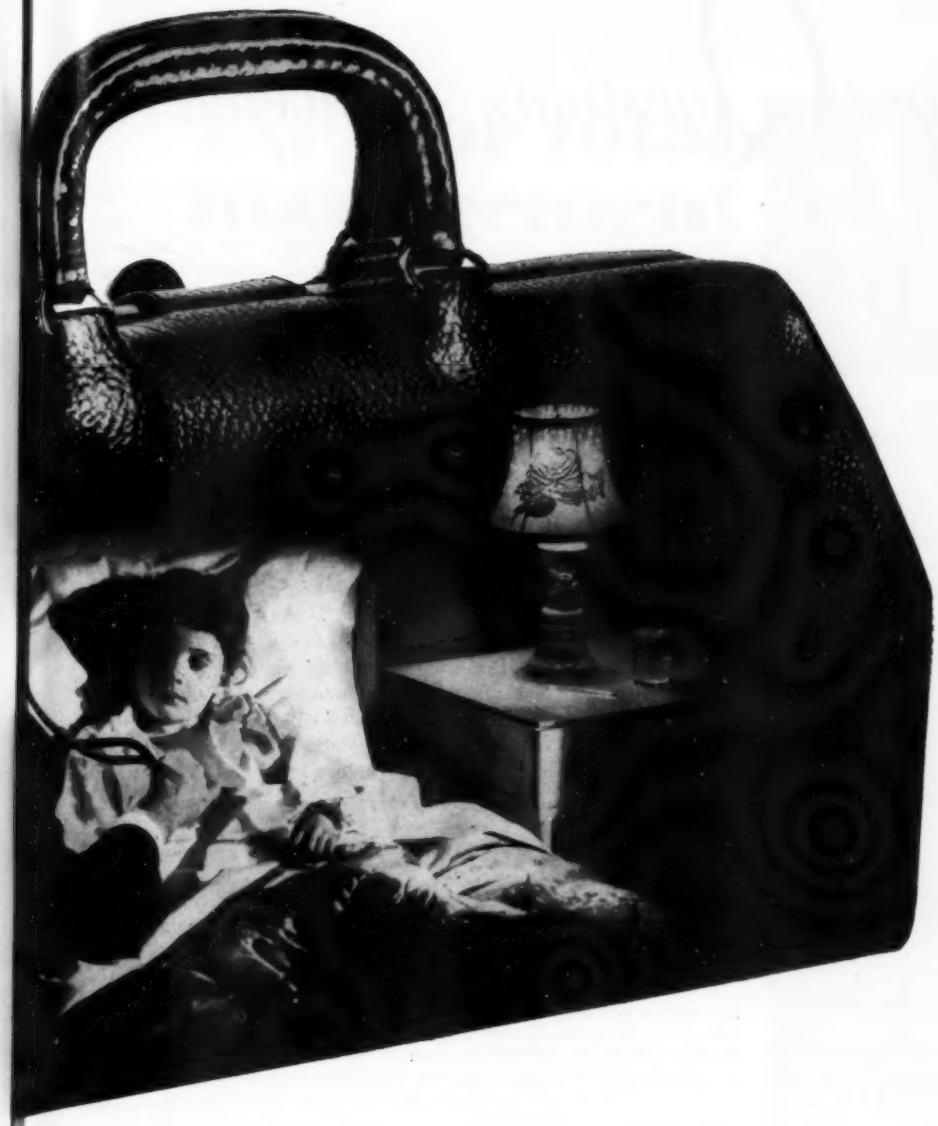

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• INTOLERANCE TO DIGITALIS

Q. When practicing in Europe, I was familiar with the rectal administration of digitalis. I have had patients in this country who do not tolerate digitalis when orally administered. Why is rectal administration of the drug not common here?

M.D.—New York

A. Intolerance to digitalis, shown by loss of appetite, nausea and vomiting, is due to the amount of digitalis in the blood and its effect on the vomiting center in the brain. This reaction is not associated with the effect of digitalis on the gastric mucosa. If a patient cannot tolerate a certain dose of digitalis, too much of it is concentrating in his blood stream. Therefore, the evidences of intolerance to the drug will not be reduced if the same amount is given and absorbed by rectal administration.

• REMOVAL OF FACIAL HAIR

Q. What is the best local and systemic treatment for excessive facial hair on middle-aged women?

M.D.—Ohio

A. The only treatment for excessive hair growth is tricholysis, which is removing the hair with a small instrument. This work is now being done in most large cities by specialists who must be qualified by a board of trichology.

Of course, one must always consider the rarer conditions in which any excess of facial hair on a middle-aged woman may be due to some endocrine disturbance of the adrenal apparatus or to chronic porphyrinuria.

• PAPANICOLAOU SMEARS

Q. A laboratory which does Papanicolaou smears of cervical specimens requires fixation of the specimen in an alcohol solution, while a second laboratory requires air drying only. Which treatment will give the best results?

M.D.—Pennsylvania

A. Preservation of cells for cytologic study is best obtained by immersing the smear while still wet in a solution of equal quantities of ether and 95 per cent alcohol. The smear should not be allowed to dry before being immersed.

• SPASTICITY AND ATHETOSIS

Q. Is resection of the posterior roots of the spinal cord still being used to treat spasticity and athetosis? If not, why was it abandoned?

M.D.—Oregon

A. Spasticity and athetosis have never been treated by section of the posterior roots of the spinal cord as these carry only sensory fibers. In the past, anterior roots have been sectioned and peripheral nerves partially sectioned.

At present, certain areas of the brain are being investigated, and surgery is being performed on the basal ganglion and the cerebral peduncles in patients who have severe dystonic or athetosic movements. In selected cases, section of the peripheral nerves will sometimes partially relieve spasticity. Certain new drugs are being investigated for treatment of this condition; chlorpromazine has proved efficacious in a few cases, but it is not applicable in all cases.

(Continued on page A-24)

new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions

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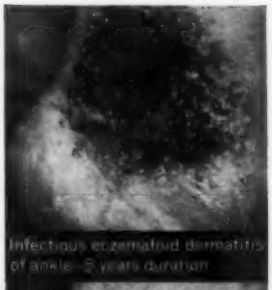
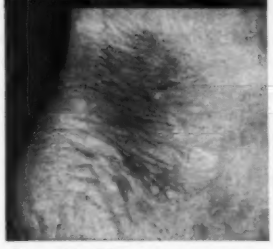


Infectious eczematoid dermatitis of ankle 3 years duration



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> **"Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[8]**

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Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Sheimire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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• BRONCHIECTASIS

Q. A 40 year old woman had a lobectomy in December 1956 for bronchiectasis of the lower lobe of the left lung. Examination of the tissue confirmed the diagnosis; bronchograms showed chronic bronchitis of the lower lobe of the right lung. In January 1957, bronchograms revealed minimal bronchiectasis of the lower lobe of the right lung. Repeat bronchograms in July 1957 showed no improvement, and the lower lobe of the right lung was excised two months later. Pathologic examination revealed marked chronic bronchitis. Bronchograms done in September 1958 showed marked bronchiectasis of the middle lobe of the right lung. The lingular bronchial ramifications were at least partially obstructed (the lobe did not fill, but it was not collapsed).

At present, the patient's cough is aggravated by work and exercise, and sometimes produces white to yellow mucoid sputum. Wheezing occurs almost daily and becomes worse with exercise; she cannot tolerate extra activities. She has some pain in her right side, but has dyspnea only when hurrying. Her vital capacity is now 51 per cent of normal; her total inspiration is 49 per cent of normal, and her one second vital capacity is 45 per cent of her total. A surgeon proposes excision of the middle lobe of the right lung. What do you recommend?

M.D.—Michigan

A. Information on this case is not too complete, but I suggest a rather long and intensive medical treatment, using inhalation therapy and antibiotics, with the exact drug determined by sputum culture findings. In three or four months, the patient's condition should be re-evaluated and new bronchograms made.

• DIAGNOSTIC CURETTAGE

Q. A 29 year old patient, Gravida IV, Para IV, who had severe poliomyelitis at the age of 15 and now walks with crutches, has had four cesarean sections. She now has menorrhagia of three months' duration. Would there be any special hazard in performing a diagnostic dilatation and curettage?

M.D.—Wisconsin

A. There is no contraindication to diagnostic curettage in this patient, and it definitely should be performed.

• CANCER DETECTION

Q. Is the routine use of Schiller's test as effective as the Papanicolaou staining method in screening for cancer of the cervix?

M.D.—Philippines

A. No. Although Schiller's test is useful in identifying the area from which biopsy material is to be collected, it should not replace microscopic examination of tissue.

• TRICHINOSIS

Q. What treatment would you suggest for trichinosis? Is HETRAZAN® of any value? If ACTH is used for a systemic reaction in cases of severe infection, has it any permanent effect?

M.D.—British Columbia

A. The treatment for trichinosis is still unsatisfactory, although some of the new drugs that have been effective against roundworms may be tried. It is possible that the action of these agents may rid the intestinal tract of some of the worms before they complete their egg-laying function. I suggest giving 200 mg. Delvex after meals for five days or a single dose of 4 mg. ANTEPAR® (piperazine citrate), repeated two or three times at two to three day intervals if necessary. Either of these drugs is preferable to Hetrazan. No known drug is effective against the larvae after they have migrated into the body tissues. The mortality in the acute phase is approximately 5 to 30 per cent.

The steroid hormones are helpful in managing shock or prostration, which can occur with an overwhelming infection. They are not curative, but they may combat shock until the body's defenses can overcome the toxemia from the migrating larvae. The suggested dosage is 20 to 40 units ACTH in a 5 per cent glucose solution given intravenously over a 24 hour period or 20 units ACTH every six hours administered intramuscularly. If the patient can swallow and is not vomiting, 100 mg. cortisone may be given orally every eight hours for a few days. Administration of hormones should be decreased and finally discontinued as soon as shock is controlled. This eliminates the risk of aftereffects due to the use of steroid hormones. (Aikawa, J. K.: Trichinosis. In Conn, H. F.: Current Therapy. Philadelphia and London, W. B. Saunders Company, 1958, pp. 59-60.)

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

RE-EXAMINATION FOR PHYSICIANS

Congress of Medical Education and Licensure:

• Periodic re-examination of licensed physicians or postgraduate education, or both, should be required for continuing membership in organized medicine. Such a program would stimulate practicing physicians to keep abreast of important developments in medicine.—Dr. Gunnar Gundersen, LaCrosse, Wis., president, American Medical Association.

• The changing social character of the student probably accounts in part for his change in attitude toward medicine as a profession. Modern youth seems less given to dedicated pursuits and the desire for achievement. Idealism is on the wane. Conformity and homogeneity characterize the age, and there is every promise that the trend will not be interrupted in the future.—Dr. John A. D. Cooper, assistant dean, Northwestern University Medical School, Chicago.

PERSONAL BONE MARROW BANKS STUDIED

Western Society for Clinical Research:

• Bone marrow was aspirated from the iliac crest of four patients and stored in chests of DRY ICE®. The patients then received whole-body radiation for malignant seminoma. Platelet counts dropped below 60,000. The stored marrow was reinfused intravenously on five occasions following completion of radiotherapy. One patient died of acute radiation injury six days later. In the other three, the bone marrow became hyperplastic within three weeks, and peripheral blood counts showed recovery within six weeks. The method is currently used in treating lymphomas and radiosensitive tumors.—Dr. N. B. Kurnick, University of California School of Medicine at Los Angeles.

THEORY OF FOCAL INFECTION

Chicago Dental Society:

• A severe eczematous dermatitis of the hand and forearm that did not respond to standard dermatologic therapy was improved following periodontal treatment. When the periodontal condition was neglected by the patient, the skin eruptions recurred. The patient has maintained proper oral health during the last five years, and the dermatologic lesions have not reappeared. Statistical data on the incidence of focal infection in 1000 dermatologic patients are being analyzed.—Dr. Allen G. Doner, Northwestern University, and Dr. Richard Oliver, University of Illinois College of Medicine, Chicago.

Genetics and cancer

Symposium on fundamental cancer research, University of Texas M. D. Anderson Hospital and Tumor Institute, Houston:

- Development of resistance to chemical agents in leukemia may be based on changes akin to mutations in the chromosomes of the malignant cells. The chromosomal make-up of several drug-resistant sublines of mouse leukemia L 1210 was found different from that of the parent line.—Dr. John J. Biesele, University of Texas Southwestern Medical School, Dallas.
- A daughter of a patient with mammary cancer is no more likely to have cancer than is any other patient. However, if cancer should develop in the former, it is more likely to be in the breast. There is no evidence that a causative virus is transmitted in humans through nursing.—Dr. Madge T. Mackin, Ohio State University College of Medicine, Columbus.

Continuous corticosteroid therapy effective

American Academy of Allergy:

- Small daily doses of corticosteroids are effective over long periods. Good results were achieved in 50 patients with chronic intractable asthma who were maintained over a period of three to eight years on a daily dose of 10 mg. prednisone or prednisolone or an equivalent dose of the newer compounds. When compared with intermittent therapy, results showed a smoother clinical course and less physical difficulty.—Dr. Walter L. Winkenwerder, The Johns Hopkins University School of Medicine, Baltimore.
- Bronchiolitis in infancy should be regarded as a condition which often is followed by the development of allergic respiratory disease, particularly asthma. A follow-up of 100 children with bronchiolitis seen between 1950 and 1957 showed that asthma eventually developed in 32 per cent.—Dr. Heinz J. Wittig, department of pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.
- Asthma and other allergies in themselves are not indications for tonsillectomy. Tonsillectomy will not cure allergic diseases, and it may induce new allergic manifestations in allergic patients.—Dr. Mary F. Lerner, Brooklyn.
- When cystic fibrosis is associated with allergy, the existence of the cystic disease may be obscured by the symptoms of allergy.—Dr. Thomas E. Van Metre, Jr., The Johns Hopkins University School of Medicine, Baltimore.

Psychic energizers

Postgraduate Educational Conference, University of California School of Medicine, Berkeley-San Francisco:

- Advantages of psychic energizers over electroshock in the treatment of depressions include preference by patients, safety, and less cost. The amine oxidase inhibitors also provide pharmacologic evidence of what may be the basic chemical pathology in certain cases of depression, whereas electroshock is a nonphysiologic treatment, and its mode of action is very poorly understood.—Dr. Nathan Kline, Rockland State Hospital, Orangeburg, N.Y.

Smallpox vaccination for physicians

Symposium on infectious disease problems, Medical Education for National Defense:

- Experience has shown that a physician traveling in foreign countries can become an unknown carrier of smallpox. Members of hospital staffs should be immunized every three years.—Dr. Alexander D. Langmuir, Communicable Disease Center, Atlanta.

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Laboratory Aids in Diagnosis of Bleeding Disorders, Part 2

SHERWOOD P. MILLER†

City of Hope Medical Center, Duarte, California

In the first part of this discussion, published in this column last month, various tests were recommended for diagnosing bleeding disorders due either to a capillary-platelet defect or to a defect in plasma coagulation factors. Other important procedures which may be used for investigating coagulation disorders are the prothrombin consumption test,[15] the whole blood coagulation test and the thromboplastin generation test.

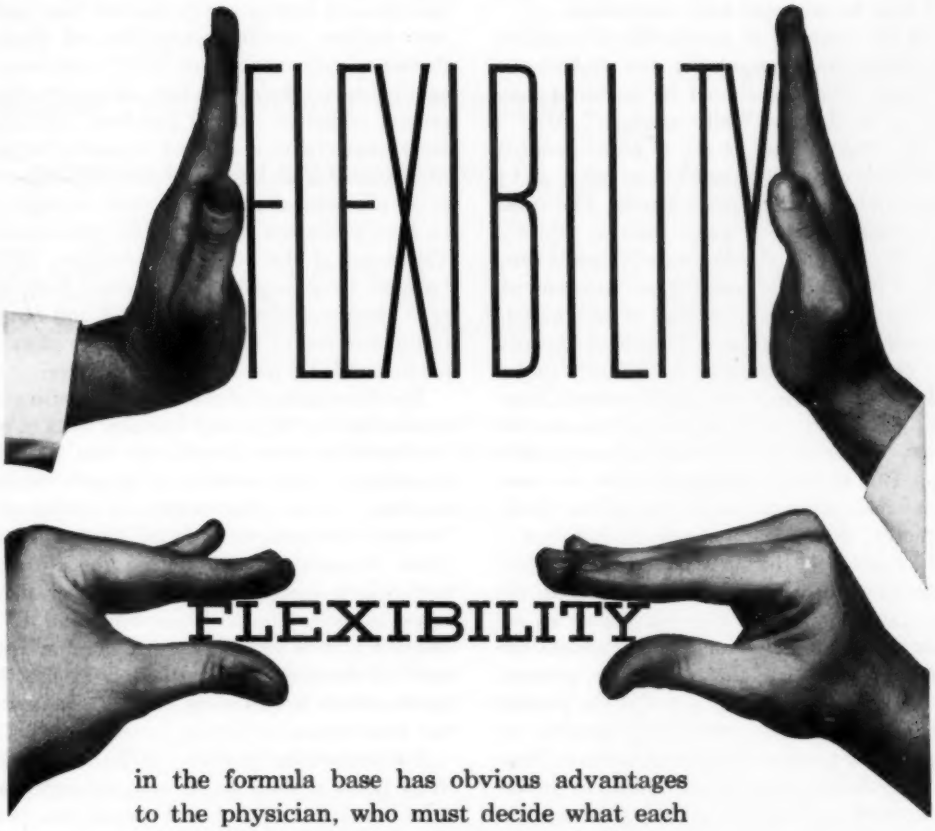
The first test is best understood if one realizes that thromboplastin must be present in adequate amounts for conversion of prothrombin into thrombin (figure 2, part 1). In the presence of normal amounts of thromboplastin, virtually all the prothrombin in the plasma will be consumed. Thus, a comparison of prothrombin levels in the plasma and serum of the same person will reveal less than 10 per cent of the original level to be present one hour after clotting. Since one cannot measure prothrombin directly in serum (no fibrinogen remains to be clotted), one must add a prothrombin-free source of fibrinogen. This is most simply accomplished by the use of barium sulfate-adsorbed plasma, which, in addition to fibrinogen, has an excess of proaccelerin present. When the Quick time on the serum is done with equal volumes of serum, barium sulfate-plasma, tissue thromboplastin and calcium chloride, the mixture should not coagulate in less than 35 seconds, indicating that almost all the prothrombin was consumed in the process of clotting. When the time of coagulation is less than 25 seconds, prothrombin consumption has been inadequate, and one may conclude that a significant disturbance of the first stage of coagulation (evolution of thromboplastin) is present.

Such a disturbance of the first stage of coagulation is found in hemophilia and related disorders. In this group of conditions, the defect lies in the absence of one of the thromboplastin precursors. In studying these defects it is important to remember that the disturbance occurs two steps removed from the only reaction that it is possible to measure. Consequent-

(Continued on page A-38)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

†Formerly Chief, Coagulation Service, City of Hope Medical Center, Duarte, California; now in Staten Island, New York.



in the formula base has obvious advantages to the physician, who must decide what each infant needs, and when changes are indicated. An evaporated milk formula is a prescription formula, permitting the physician to adjust

... the type and amount of carbohydrate

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ly, conclusions are based on indirect evidence and must be accepted with reservation.

At this point it is worthwhile to consider the whole blood coagulation test and its significance. The test should be performed according to the Lee-White method.[16] After a careful venipuncture, 2 ml. of blood is introduced into each of two small glass tubes, and a stop watch is started immediately. The tubes are maintained in a water bath at 37° C.; after five minutes, the first tube is tipped carefully to determine if coagulation has occurred. If it has not, this is repeated at one minute intervals until the tube is completely invertible. Then the second tube is carefully tipped and the process repeated at 30 second intervals. The time at which the second tube is completely invertible is recorded as coagulation time. This test is a measurement of the overall intrinsic coagulation ability of the blood. Normally, coagulation occurs in between 5 and 12 minutes. During this period, the three stages previously described have occurred; the first stage is the most time-consuming of all. Since only minute amounts of platelets are necessary to initiate the coagulation process, the test is virtually independent of the platelet level. It is, however, moderately sensitive to levels of the plasma coagulation factors. Thus, the coagulation time will be normal in thrombocytopenic purpura but greatly prolonged in hemophilia and allied disorders. Conversely, since no disturbances in the tissue thromboplastic properties and the blood vessels have been found in patients with hemophilia, they have normal bleeding times but prolonged coagulation times. In part 1 of this discussion, I indicated that the Quick prothrombin time is performed in the presence of a tissue thromboplastin extract, which short-circuits the first stage of coagulation. It may be expected, therefore, that disorders of the first stage of coagulation will have normal Quick times as, in fact, they do; however, the prothrombin consumption will be abnormal, as previously indicated.

These tests, as well as those discussed last month, are all indirect. We must turn to the thromboplastin generation test in order to demonstrate more precisely the defect in hemophilia and its related disorders. For this purpose we will consider only the two most common entities, classic hemophilia and plasma thromboplastin component (PTC) deficiency[17] or Christmas disease.[18] Both disorders may present identical clinical pictures, including the characteristic sex-linked recessive heredity. Recent studies have indicated that from 10 to 33 per cent of cases previously thought to be hemophilia are, in fact, PTC deficiencies. The status of the other abnormalities (PTA [plasma thromboplastin antecedent] deficiency,[19] Hageman factor deficiency,[20] and Stuart factor deficiency[21]) is somewhat less clear at present and will not be considered here.

The development of the thromboplastin generation test by Biggs and Douglas[22] has made it possible to study directly the first stage of coagulation (the evolution of plasma thromboplastin) and, consequently, to distinguish between the several varieties of the hemophilic diseases. In considering the two defects which comprise the majority of these cases, namely, classic hemophilia and PTC deficiency, it is necessary to be familiar with some of the simple properties of the specific factors which are missing respectively in the two disorders.

Antihemophilic globulin (AHG) is a relatively labile protein which is apparently consumed during the process of coagulation. It is not adsorbed from plasma by the common adsorbing agents. Plasma thromboplastin component, on the other hand, is relatively stable, persists in serum following coagulation of blood, and is rather completely removed from plasma by inorganic absorbents. Thus, these two factors may be readily separated from each other by means of adsorbing the plasma in question to yield an AHG source and by obtaining serum from the same patient to yield a PTC source. It is then possible to determine which of these factors is missing in a given patient. The other reagents necessary for thromboplastin generation include platelets (which may be separated readily from blood by differential centrifugation and washed free of contaminating plasma proteins by saline) and calcium chloride.

(Continued on page A-40)

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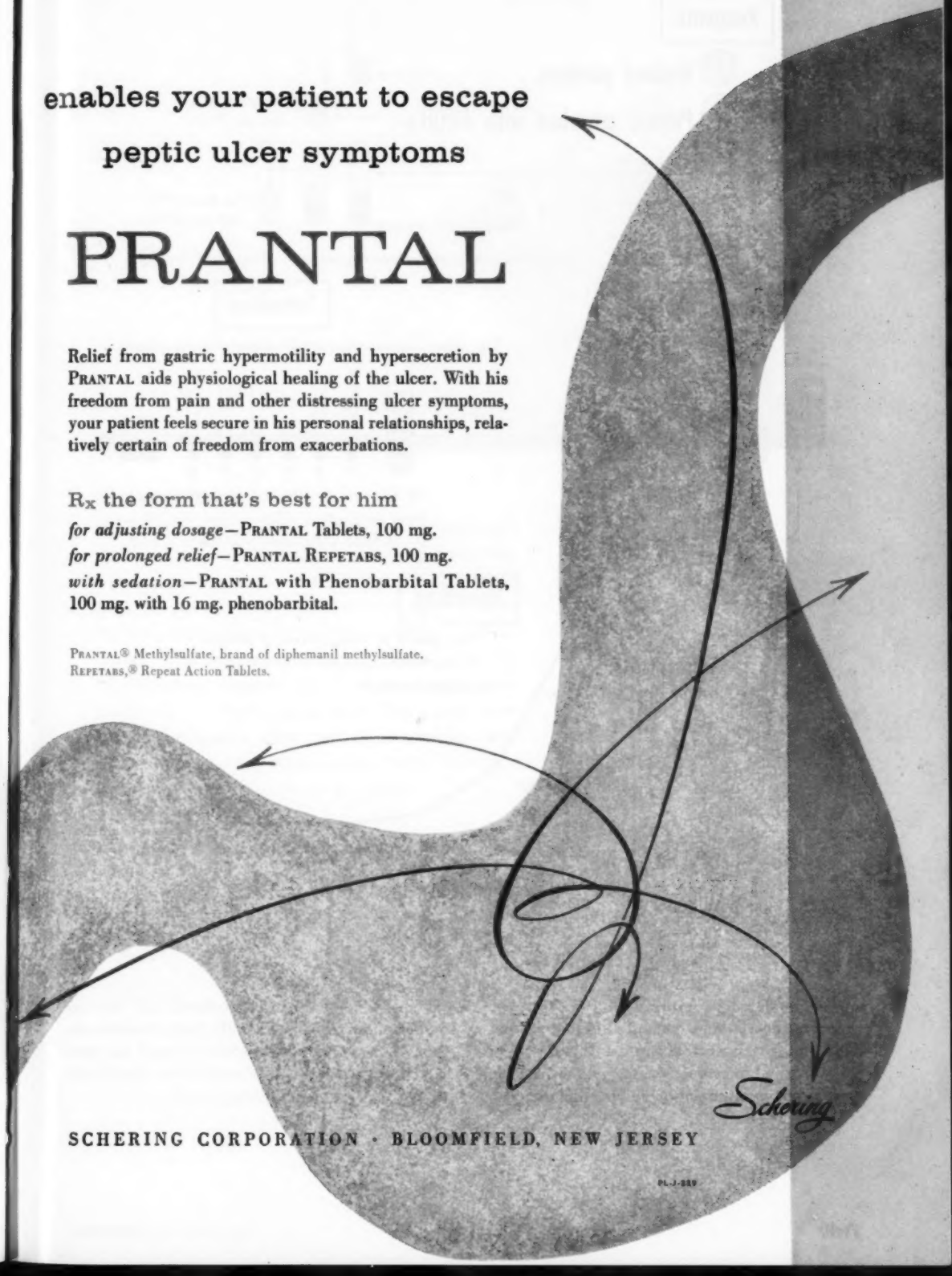

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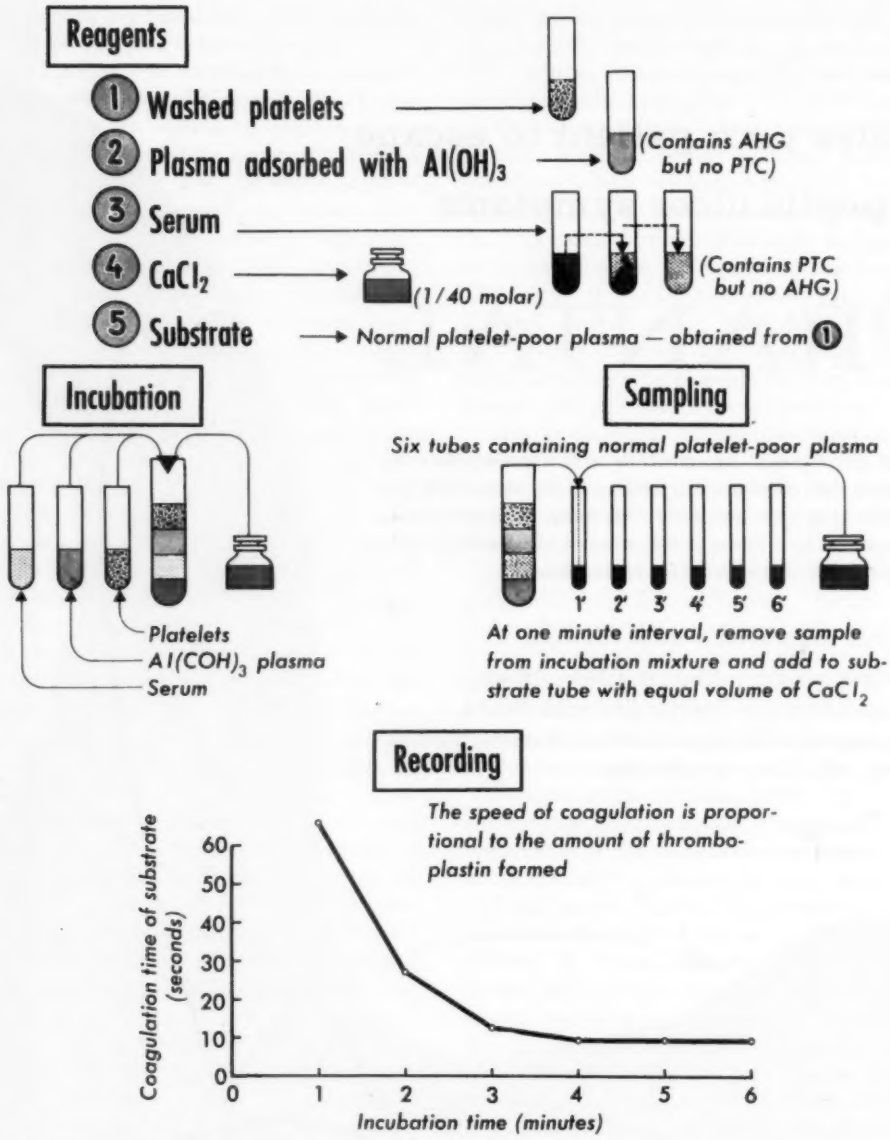

FIGURE 4. The thromboplastin generation test.

(Figures are numbered consecutively throughout both parts of this article.)

As indicated in figure 4, the necessary reagents are prepared from the patient in question and from a normal control. Equal volumes of adsorbed plasma, serum, platelet suspension and calcium chloride are incubated at 37° C. (It should be mentioned that this incubation mixture is virtually free of prothrombin, because neither adsorbed plasma nor normal serum contains this material in significant

(Continued on page A-42)

Enuresis

In the physically normal older child, persistent bed-wetting is often the revealing symptom of an anxiety state. Thus, the alleviation of psychic tensions is an important step in promoting nocturnal sphincter control. After using EQUANIL as a management adjunct, McClendon[1] reports: "Out of the sixty cases followed . . . there have been forty-one complete successes, ten partial successes and nine failures. . . . These cases were selected because of the failure of all other measures. . . ."

1. McClendon, S.J.: Arch. Pediat. 75:101 (March) 1958.

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amounts.) Consequently, the second stage of coagulation does not occur in this incubation mixture. As the reaction proceeds, samples of the mixture are withdrawn at one minute intervals by means of a pipet and are added to a separate series of tubes containing small portions of normal platelet-free plasma. This plasma, containing presumably normal amounts of prothrombin, proaccelerin, proconvertin and fibrinogen, will clot with a speed proportional to the amount of thromboplastin added to it. In order to neutralize the citrate of the substrate plasma sample, an additional aliquot of calcium chloride is added simultaneously with the incubation tube sample, and a stop watch is started. When coagulation occurs in the substrate tube, the watch is stopped. In many ways this subtest resembles a Quick test in which the variable factor is the thromboplastin concentration rather than the prothrombin concentration, as in the more usual form of the test. The speed of coagulation will be inversely proportional to the amount of thromboplastin generated in the incubation tube at the time at which the sample was withdrawn.

While little or no physical change is seen in the incubation mixture, it is evident that a powerful thromboplastic factor is being evolved, because with successive samples the coagulation time of the substrate mixture shortens to a minimum of about 10 seconds, usually achieved after three or four minutes of incubation. These substrate coagulation times may be plotted against the incubation time, as shown in figure 4, and will reveal the rate and amount of thromboplastin which have been evolved. When this test is performed using the three reagents (adsorbed plasma, serum and platelets) from a normal person, maximal activity is generated in three or four minutes and is sustained at this level for eight or more minutes. When the reagents are derived from a hemophilic patient, little or no activity is generated even after 8 or 10 minutes. It is possible, by making appropriate combinations of a hemophilic patient's and a normal person's reagents, to determine which one of the patient's reagents is responsible for the defective thromboplastin generation. When the plasma reagent from the classic hemophilic patient is used with normal serum and platelets, generation is defective. But when the patient's serum is used (with normal plasma and platelets) or when the patient's platelets are used (with normal serum and plasma) generation is normal. Therefore, the defect lies in the plasma reagent, which should contain antihemophilic globulin, and the disease is classic hemophilia. In the case of PTC deficiency, the defect lies in the serum reagent. It is thus possible to distinguish between these two diseases with identical clinical, hereditary and laboratory patterns on the basis of this test alone, without reference to other cases of coagulation defect.

The use of the test in detecting other disorders (PTA deficiency, etc.) in the first stage of coagulation depends on knowledge concerning the properties of the missing factor. In most of the other disorders described, the factor in question appears to be removed from normal plasma by adsorption with barium sulfate or aluminum hydroxide and to be present in normal serum. It is absent, of course, in the patient in question. One therefore tends to find the abnormality on the "serum side." The plasma thromboplastin antecedent (PTA) factor is reportedly present to some extent in both adsorbed plasma and normal serum; consequently, one does not find defective thromboplastin generation in this disorder unless one uses both patient's plasma and serum in the same incubation mixture. The test is also of value in detecting functional disorders of platelets in which there are inadequate or nonfunctioning platelet thromboplastic factors. In this case, although normal numbers of platelets will be present, the thromboplastin generation test will be abnormal when the patient's washed platelets are used in the generation mixture.

Comment

At this point, our investigation of coagulation disorders has become rather involved, and we are studying abnormalities which are two steps removed from the final reaction which we observe. Nevertheless, by paying careful

(Continued on page A-44)

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TABLE 2

OUTLINE FOR INVESTIGATING BLEEDING DISORDERS

I. History and physical examination

II. Bleeding time, tourniquet test, platelet count, coagulation time, Quick's test

A. Bleeding time, Tourniquet test, Platelet count } abnormal — Coagulation time, Quick's test } normal

1. Platelets low (thrombocytopenia)
   a. Marrow megakaryocytes adequate
      (1) History negative—idiopathic thrombocytopenic purpura
      (2) History of drug ingestion—thrombocytopenia due to drug sensitivity
   b. Marrow megakaryocytes absent—secondary thrombocytopenic purpura
2. Platelets normal in number
   a. Abnormal morphology, defective clot retractions, etc.—thrombasthenia
   b. Abnormal TGT (thromboplastin generation test) (platelets)—platelet functional defect

B. Bleeding time, Tourniquet test, Platelet count } normal — Coagulation time—prolonged or normal; Quick's test—normal

1. TGT differentiates
   a. Hemophilia—abnormality in plasma reagent
   b. PTC deficiency—abnormality in serum reagent
   c. PTA deficiency—abnormal when both plasma and serum reagents are used

C. Bleeding time, Tourniquet test, Platelet count } normal — Coagulation time—normal or prolonged; Quick's test—abnormal

1. Coagulation time indefinitely prolonged—afibrinogenemia
2. Coagulation time—normal or prolonged slightly

Deficiency of prothrombin, proaccelerin or proconvertin*

*See table 1, part 1 to differentiate.

attention to details, it is possible to obtain quite precise and valuable information regarding the defect. A general plan for investigating bleeding disorders is summarized in table 2.

The therapeutic implications of making a precise etiologic diagnosis of a hemorrhagic defect are apparent without belaboring the point. While additional refinements will yield further information regarding the coagulation process in general and in a given patient as well, a precise diagnosis is possible with only a minimal amount of equipment. One must be willing to devote sufficient time to assure accuracy in the performance of the tests.

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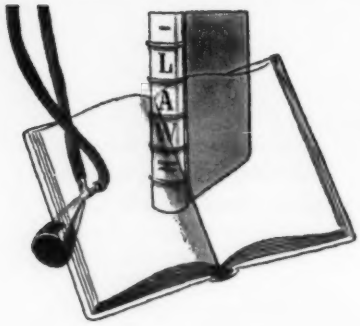

Forensic Medicine

Malpractice: Recent Trends

E. C. BRYSON*

Duke University, Durham, North Carolina

A PATIENT enters the hospital for routine surgery. During the operation, while the patient is under anesthesia, the surgeon discovers a condition which neither he nor the patient had anticipated. If this condition does not constitute an emergency which necessitates immediate action, is the surgeon liable to the patient if he proceeds to correct the condition, regardless of the skill used or the benefits conferred?

The early common-law view of such a situation held that the patient's consent should specifically and unequivocally authorize the surgery which was to be performed, and that there must be actual consent to any extension of the operation. Later decisions indicate a tendency to relax this rule and to recognize a so-called implied consent or the surgeon's privilege to modify or extend the operation when he discovers some other condition which, in his best medical judgment, calls for immediate action because it represents an imminent threat to the patient's life or will gravely or irreparably injure his health.

The law seems well settled that an operation is a technical battery or trespass, and that before extending an operation in the absence of an emergency the surgeon must first obtain the consent of the patient or of someone authorized to act for him. In the case of Scholendorf vs. N. Y. Hospitals, 211 N. Y. 125, 105 N. E. 92, Justice Cardoza ruled as follows:

> Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages. . . . This is true, except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained.

In view of the advances in medical specialization, new technics and surgical procedures, and the desirability that neither physician nor surgeon be afraid to act in the best interests of his patient, it has been suggested that these rules do not adequately protect the physician or surgeon and that he should be permitted to proceed with impunity, even in the absence of an emergency condition.

In a case of first impression (Tabor vs. Schobee, 254 S. W. 2d 474 [1951]), the Kentucky Court of Appeals refused to accept this principle. In this case a 20 year old patient submitted to an operation for appendicitis. During the operation, the surgeon discovered that the patient's fallopian tubes were full of pus, swollen, and sealed at both ends. The surgeon removed the tubes, although he was, of course, unable to obtain the patient's consent

(Continued on page A-54)

*Attorney for Duke Hospital, Duke University, Durham, North Carolina.

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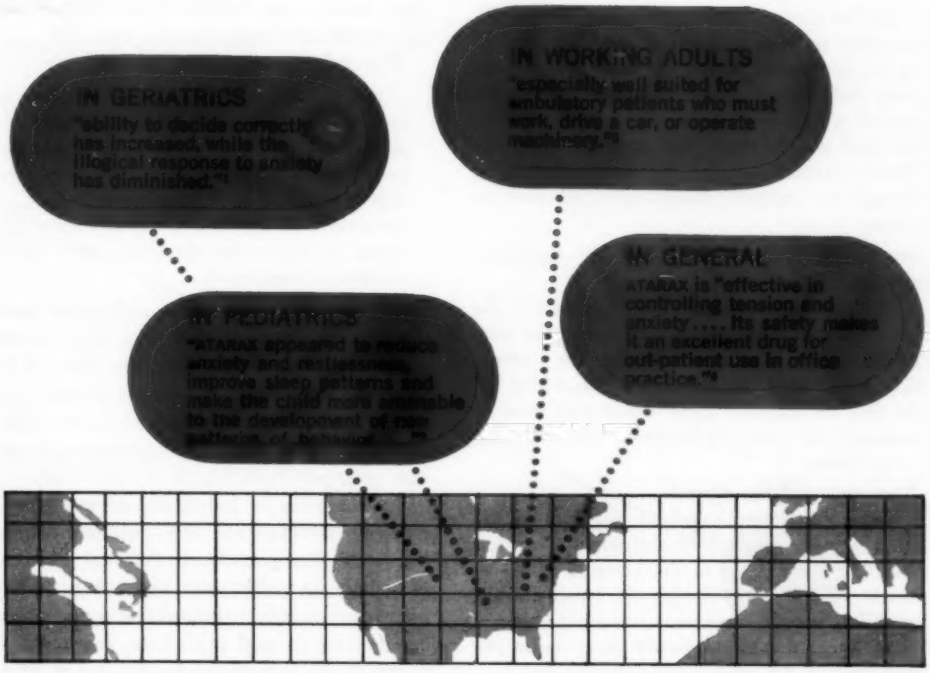
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and did not obtain her stepmother's consent. He proceeded on the theory that the tubes would have had to have been removed "within six months anyway, if I was not mistaken."

Testimony of his professional colleagues approved the surgeon's decision. The trial court instructed the jury:

> [If the surgeon] discovered that her fallopian tubes were in a diseased condition and if, in his judgment, in the exercise of ordinary care and skill . . . such condition if not removed would have endangered the plaintiff's life and health, then [the surgeon] was justified in removing the diseased tubes, even though no express consent was obtained or given.

In reversing this instruction, the appellate court said:

> The instruction does not impress on the jury that the emergency must exist at the time of the operation. The wording of the instruction is so broad the jury could reasonably infer that the diseased tubes would only have to endanger the patient's health or life sometime in the future.

The court further stated:

> The evidence indicated the removal of the tubes probably would be necessary soon and that their remaining in the body in their infected condition was dangerous, but it did not establish that their removal was an emergency in the sense that death would likely ensue immediately if the tubes were not removed. . . . Although delay in their removal might have proved harmful, even fatal, there still was time to give the parent of the patient time to weigh the fateful question.

Two more recent decisions in similar cases, handed down by state appellate courts in opposite parts of the country, should be of interest to members of the medical profession.

The Kennedy Case

In the case of Kennedy vs. Parrott, 243 N. C. 355, 90 S. E. 2d 754, the North Carolina Court of Appeals rendered a decision which should be gratifying to all surgeons. In this case the plaintiff consulted the defendant-surgeon, who diagnosed her condition as appendicitis and recommended an appendectomy, to which she agreed. During the operation the surgeon discovered and punctured some enlarged cysts on the patient's left ovary. Although the action was brought to recover damages for personal injuries resulting from the surgeon's alleged negligence, it actually resolved into an action for damages proximately resulting from the unauthorized cyst puncture, which was considered an alleged technical assault or trespass on the plaintiff.

The defendant-surgeon testified:

> I say they [the cysts] were dangerous. I can't say how long it would have been before she would have had to have an operation; it possibly could have been two or three months before it would have been necessary. . . . It is possible if I had not done anything to this ovary or ovaries that she might never have had to have an operation.

Expert witnesses for the defendant testified that the puncture of the cysts was in accord with sound surgical procedure, "that it is the accepted practice in the course of general surgery," and that if they had performed the appendectomy they also would have punctured any enlarged cysts found on the ovaries.

In affirming a judgment of nonsuit (dismissed) in favor of the defendant-surgeon, the North Carolina court reasoned that the use of anesthesia and modern operating room technics have greatly enlarged the scope of surgical operations and that, now, complete diagnosis of an internal ailment is not effected until after the patient is under the influence of anesthesia and the incision has been made.

The court further reasoned that to conform with these changes the law also must be changed in the interest of the patient and the surgeon; thus, it is necessary that the law delegate someone to act for the patient in those matters affecting his welfare in which a condition that is an essential part of the operation precludes the patient's acting for himself. The court maintained that the surgeon whom the patient himself has selected fills all of the requirements; hence, on the surgeon the law should cast such responsibility, by the legal implication that since the patient selected no one else to act for him he intended that the surgeon fulfill this office. The court said:

(Continued on page A-56)

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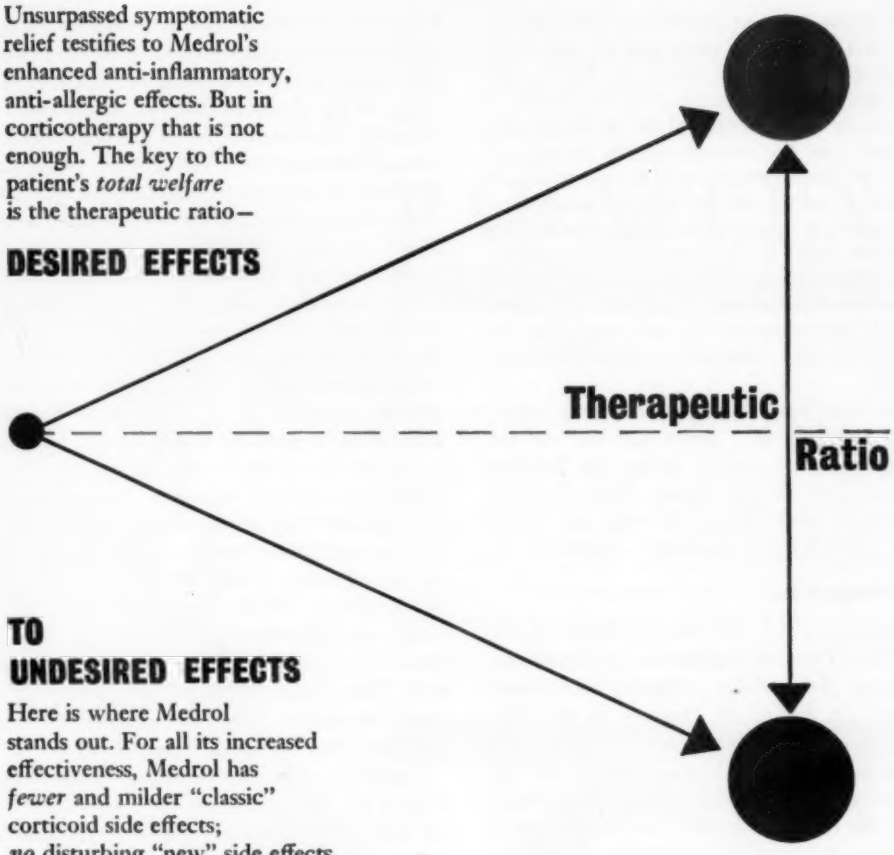

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> In major internal operations, both the patient and the surgeon know that the exact condition of the patient cannot be finally and definitely diagnosed until after the patient is completely anesthetized and the incision made. In such case the consent—in the absence of proof to the contrary—will be construed as general in nature, and the surgeon may extend the operation to remedy any abnormal or diseased condition in the area of the original incision whenever he, in the exercise of his sound professional judgment, determines that correct surgical procedure dictates and requires an extension of the operation originally contemplated.

Thus, the North Carolina Supreme Court refused to apply the "strict consent" or the "emergency" test and to define the liability of the surgeon in such terms. Instead, it authorized the performance of such an operation as good surgical procedure demands.

The Salgo Case

In October 1957, the District Court of Appeals, First District, California, handed down a decision (Olga Salgo, Admrx., vs. Leland Stanford, Jr. Board of Trustees et al., 317, P-2a 170) reversing one of the largest malpractice judgments in history ($250,000, reduced to $213,355). The action was brought against the Leland Stanford University Board of Trustees and Stanford University Hospitals, which are one entity, and Dr. Frank Gerbode. The case was of such interest that *amicus curiae* briefs were filed on behalf of the appellants by the Regents of the University of California and on behalf of Dr. Gerbode by the American College of Surgeons.

Several questions which long have perplexed those interested in medicolegal problems were involved in this case and, as in the Kennedy case, were answered in a manner which should be gratifying to the members of the medical profession.

The Salgo case arose from alleged negligence in the performance of aortography. Briefly stated, the evidence was as follows:

Salgo, who had been under a physician's care for approximately one year, was referred to Dr. Gerbode, a specialist in the surgical treatment of arterial diseases. On examining Salgo, Dr. Gerbode found evidence of serious circulatory disturbance, indicating a possible block in the abdominal aorta. He advised Salgo of his findings and recommended that he enter the hospital for a thorough evaluation of his condition. Although he did not explain all the various possibilities to Salgo, Dr. Gerbode did tell him that his circulatory condition was quite serious.

Dr. Gerbode wrote an order to the hospital x-ray department to make an aortogram of the patient, and he discussed the procedure with members of the house staff. Immediately prior to the aortography, Salgo was given an intravenous injection of 1 cc. UROKON® sodium (the contrast medium which was to be used) to determine whether he was sensitive to it. Sensitivity was not apparent. The needle was then inserted into the aorta and 30 cc. Urokon was injected. A series of x-ray films was taken; on consultation, it was decided to take additional x-rays. While the needle was still in place, an additional 20 cc. Urokon was injected. The entire procedure seemed quite normal. When Salgo awoke the next morning, his lower extremities were paralyzed. His condition was described as permanent.

Liability—One of the several theories advanced by Salgo was that Dr. Gerbode should be held liable for the hospital team's negligence, if any, in performing the aortography. To this the court replied that there was no evidence that Dr. Gerbode either expressly or by implication agreed to perform it. In addition, evidence from other doctors indicated that it was not customary for the attending physician to perform or to be present during the aortography, and that such procedures were customarily carried out by hospital personnel. In this connection, the court said:

> When a patient is placed in a hospital, his attending physician orders many procedures to be undertaken by the hospital staff or employees. Common examples are urinalysis, blood counts and x-rays. Suppose that in extracting blood for a count the hospital personnel negligently infected the patient. It could not be contended that the attending physician was liable for that negligence. The same is true

(Continued on page A-58)

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here. The attending physician cannot be held liable for acts over which he had and could have had no control.

The effect of custom and the absence of evidence of any express or implied agreement by Dr. Gerbode to perform the aortography should be carefully noted in the discussion of this point. It also should be noted that the court was quick to point out that although a hospital furnishes a surgical team, this does not relieve the attending physician of his obligation to determine the team's competency.

Duty to disclose—Another theory advanced by the plaintiff was that he had not been informed that anything in the nature of aortography was to be performed; that is, that Dr. Gerbode had violated his "duty to disclose." On this point the trial court instructed the jury that it was the duty of a physician to inform his patient of "all the facts which mutually affect his rights and interests and of the surgical risk, hazard or danger, if any. . . ." Reversing this instruction, the appellate court stated:

> A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment. Likewise, the physician may not minimize the known dangers of a procedure or operation in order to induce the patient's consent.

However, the court then observed that the physician must place the welfare of his patient above all else:

> [He] may recognize that each patient presents a separate problem, that the patient's mental and emotional condition is important and in certain cases may be crucial, and that in discussing the element of risk a certain amount of discretion must be employed consistent with the full disclosure of facts necessary to an informed consent.

Experimentation—It should be recalled that the contrast medium used in the aortography was Urokon sodium. The manufacturer's brochure on this product stated that for translumbar aortography in an adult "10 to 15 cc. of 70 per cent Urokon is adequate" and that aortography should not be repeated within 24 hours. In Salgo's case, 30 cc. was injected initially, and 20 cc. later, a total of 50 cc. There was evidence that doses larger than those recommended by the manufacturer's brochure were usually given. The court stated:

> It [the brochure] cannot establish as a matter of law the standard of care required of a physician in the use of the drug. . . . The mere fact of a departure from the manufacturer's recommendation where such departure is customarily followed by physicians of standing in the locality does not make the departure an experiment.

Comment

Thus, the North Carolina Supreme Court in the Kennedy case and the District Court of Appeals of California in the Salgo case, realizing that the scope of modern medical practice has been greatly enlarged and that the rules of law must be adapted to meet these changed conditions, applied the ancient Latin maxim: *Ratio est legis anima; mutata legis ratione mutatur et lex.* (Reason is the soul of the law; the reason of the law being changed, the law is also changed.)

Radiology FOR PRACTICING PHYSICIANS

Paget's Disease of Bone

PAUL C. HODGES*

MEDICAL eponyms tend to outlive their usefulness, obscuring rather than clarifying the thinking of those who use them; however, the term "Paget's disease" is a striking exception to the rule.

In the five cases published by Sir James Paget[1] some 80 years ago, the bones of the skull and legs were deformed by lesions he considered inflammatory; thus, he called the condition osteitis deformans. Modern pathologists are convinced that, whatever their basic nature may be, the lesions of Paget's disease are not osteitis. As x-ray examinations of the skull, trunk and extremities are employed with increasing frequency for diagnosing diseases of the sinuses, lungs, gastrointestinal tract, etc., many cases of unsuspected, nondeforming Paget's disease are brought to light. Since the condition is never an osteitis and often is nondeforming, the eponym is the preferable term.

Incidence

Data pertaining to the incidence of Paget's disease and to the parts of the skeleton most apt to be involved are meager and inconclusive. Gross errors in sampling are inevitable in groups as small as those that have been studied;[2,3] in addition, the degree of completeness of the autopsy or x-ray examination and the nature and extent of the selection of patients admitted to reporting institutions affect results profoundly. In my own experience, Paget's disease has been found in approximately 1 out of 1000 patients referred for x-ray examinations of all sorts. The most common sites have been the spine, pelvis, skull, femur, tibia and humerus. I have not seen lesions in the ribs, ulna, fibula, carpals, tarsals or the phalanges.

Clinical Diagnosis

By middle age, pain and stiffness in the spine and hips are so commonplace that perhaps the "silent" Paget's discovered accidentally by x-ray is merely Paget's in patients who, with fortitude, accept as incidental pain and disability for which less tough persons would have sought relief. But the full-blown disease that has been so well described and illustrated by Paget[1] himself cannot be mistaken. The skull enlarges steadily, usually asymmetrically. There is generalized kyphosis

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FIGURE 1. Paget's case 1, showing characteristic stooped position and bowing of the femur and tibia in a 68 year old patient 22 years after onset of disease and six months before death.

FIGURE 2. Drawing of the thickened calvaria revealed at autopsy of patient in Paget's case 1.

of the spine and lateral bowing of femora and tibias, if these bones are involved. The patient usually reports that an involved long bone has become progressively thicker than normal; physical examination confirms this fact and adds the information that the affected part is warmer than normal (a finding which Paget misinterpreted as evidence of infection). Persistent moderate to severe pain is usually pres-

FIGURE 3. Circumscripta or monophasic Paget's disease of the calvaria in a 53 year old man who complained of severe headache. An irregular, sharply demarcated geographical area in the vertex and occiput retains normal density; ossification has not yet occurred elsewhere. No other lesions were found at the time the skull was x-rayed, and we were not able to follow this case.

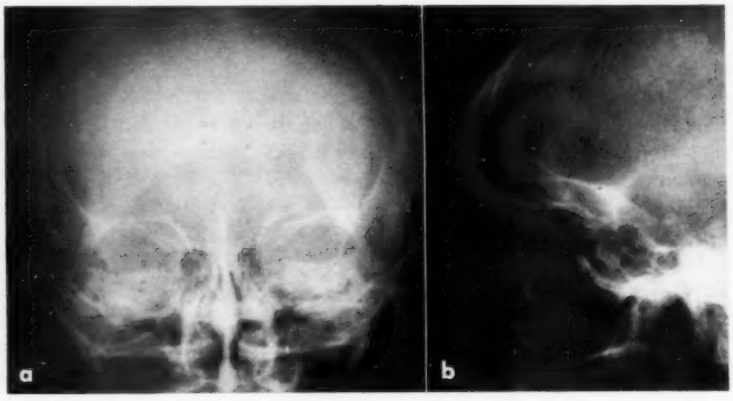


FIGURE 4a and b. Frontal and lateral views of circumscripta or monophasic Paget's disease of the calvaria showing unusual distribution of the lesions. The patient was a 48 year old woman with hirsutism and severe chronic headache who was referred for x-ray of the sella turcica. The sella turcica was normal; Paget's disease was an accidental finding.

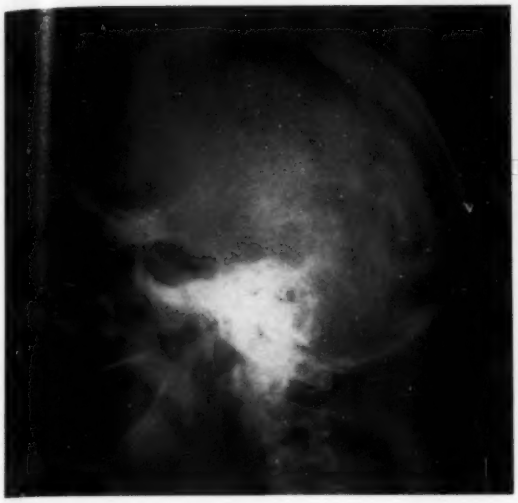


FIGURE 5. Mixed-type Paget's disease of the calvaria in a 59 year old man. Irregular dense patches of the bone of this disease are being laid down at the vertex in a zone formerly affected only with monophasic Paget's disease. Lesions were present in the right humerus and left tibia (figures 13 and 16), but not in the femora or pelvis.

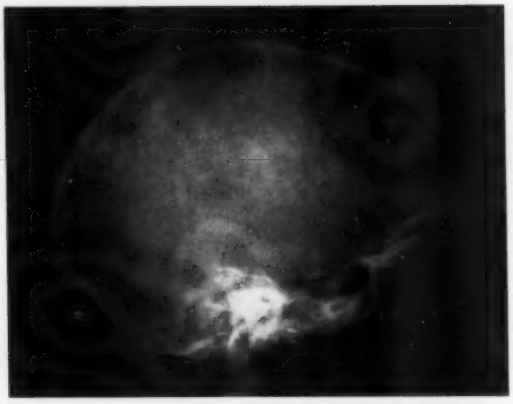
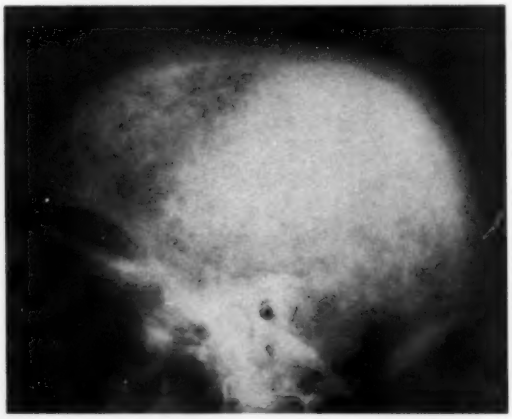


FIGURE 6. X-ray of the skull confirming the presence of silent, predominantly osteogenic Paget's disease of the calvaria in an 82 year old woman. The patient was referred for x-ray of the sinus because of pain in the left side of the face; she had a history of long-standing trifacial neuralgia. The lytic lesions, showing as irregular translucent zones about the dense patches, are in intimate contact with the plastic lesions, which constitute the so-called woolly patches.

FIGURE 7. Fully developed osteogenic Paget's disease of the calvaria in a 41 year old woman who also had Paget's disease of the spine and pelvis. The individual dense patches have fused, obliterating the lytic lesions and producing uniform thickening of the calvaria similar to that described in Paget's case 1 (figure 2).

FIGURE 8. Unusually severe osteogenic Paget's disease of the calvaria in a 55 year old woman who also had Paget's disease in other parts of the skeleton.



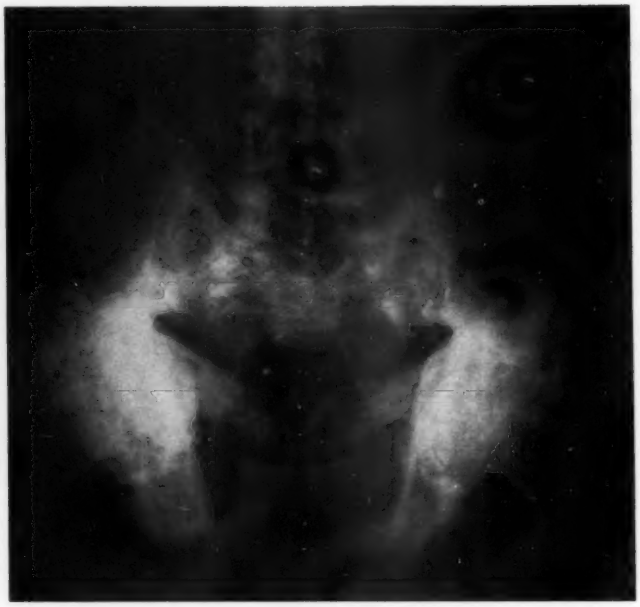


FIGURE 9. Typical severe Paget's disease of the pelvis in a 66 year old man who was deaf and infirm. The presence of Paget's disease in the spine, pelvis and skull was unsuspected until the spinal and pelvic lesions were accidentally revealed during x-ray examination of the colon. The normal trabeculae have been replaced by Phemister's "coarse, irregular, interweaving, ropelike trabeculae."

FIGURE 10. Typical lesions of conventional Paget's disease of the spine found in the bodies of L4 and 5 in a 62 year old woman. The lesions were discovered accidentally during examination of the alimentary tract; no other skeletal lesions were found.

FIGURE 11. Homogenous or eburnating Paget's disease of the spine in a 45 year old man. The body of L2 is uniformly dense. Although many investigators contend that these are not really lesions of Paget's disease, Schmorl described them. Frequently, as in this case, lesions typical of Paget's disease are found elsewhere in the skeleton.

FIGURE 12. Homogenous or eburnating Paget's disease of the spine involving the body of L2 in a 41 year old woman. Typical lesions of the disease were present in other skeletal parts.

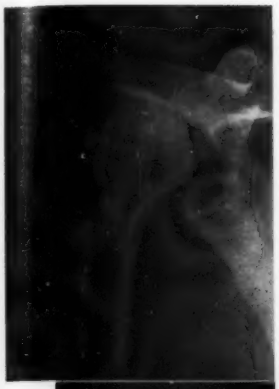


FIGURE 13. Diphasic Paget's disease of the right humerus in a 59 year old man with typical Paget's disease of the calvaria (figure 5) and of the tibia (figure 16). One zone of nonossified involved bone in the right humerus resembles a large cyst.

FIGURE 14. A solitary skeletal lesion of diphasic Paget's disease in the right humerus of a 40 year old man. The lesion was detected in bronchograms which included the heads of both humeri.

FIGURE 15. Diphasic Paget's disease of the radius in a 70 year old man who had had long-term treatment for arteriosclerotic heart disease. Paget's disease was not diagnosed until the patient noticed thickening and bowing of the right radius toward the external surface, which was caused by renewed longitudinal growth. Typical Paget's disease also was found in the skull and pelvis.

ent in the affected part, and with the passage of time the patient's stature diminishes and his hat size increases.

Gross and Microscopic Pathology

In a typically involved long bone, the shaft is broader than normal and frequently is longer as well; bowing results in the radius and tibia because of splinting by a normal ulna or fibula. The specific gravity of bone in Paget's disease is said to be lower than that of normal bone, and there is increased vascularization of the periosteum and of the bone itself. Histologically, the normal pattern of bone lamellae surrounding the haversian canals is replaced by short, thick, irregular lamellae, forming what sometimes has been described as a mosaic. Sometimes, absorption of old bone predominates, but destruction and vigorous new growth usually go hand in hand.

X-ray Findings

Skull—In the calvaria Paget's disease may be (1) purely osteolytic, (2) largely osteolytic but with definite patches of new bone production, or (3) predominantly osteogenic with little gross evidence of the destruction which preceded the production of new bone.

The purely lytic lesion is termed "circumscripta" or "monophasic," and the other two types are known as "mixed" or "diphasic." The monophasic or circumscripta stage usually is a brief phenomenon with bone production following rather promptly. Once he has encountered these three types of Paget's disease of the skull, a physician will have little difficulty in diagnosing the condition.

Pelvis—In the pelvis, bone production is so prompt and vigorous that it practically obscures the x-ray evidence of destruction, and the appearance of the new bone is highly typical. In the words of the late Dallas B. Phemister, "Normal trabecular architecture is replaced by coarse, irregular, interweaving, ropelike trabeculae." Occasionally, the lesions may be mistaken for osteogenic metastases from carcinoma of the prostate; but even in those rare cases in which x-ray differentiation cannot be made, examining the blood for acid phosphatase will settle the question. Acid phos-

FIGURE 16. Typical osteogenic Paget's disease of the tibia in a 59 year old man who also had lesions in the skull (figure 5) and in the humerus (figure 13). Biopsy of the tibia showed mosaic bone architecture; large, thickened clubbed trabeculae; fibrous marrow and multiple giant-cell osteoclasts.

FIGURE 17. Typical Paget's disease of the left femur in a 50 year old man who also had lesions in the tibia and the skull, but not in the pelvis.

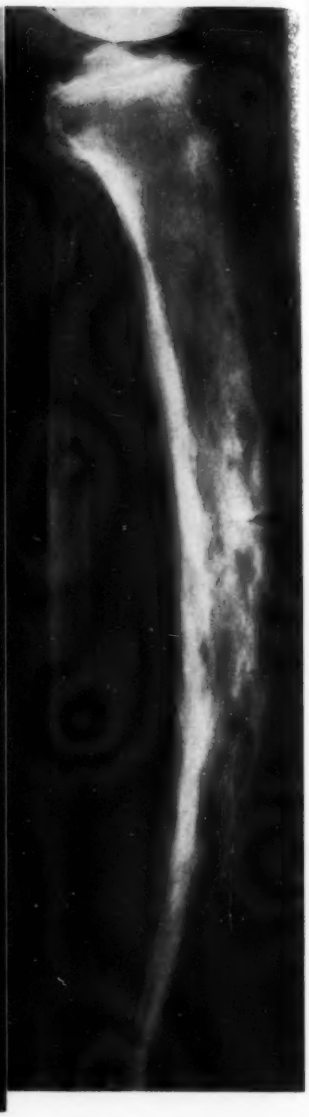


FIGURE 18. Anterior bowing and three transverse slits, interpreted as incomplete fractures or pseudofractures, produced by typical Paget's disease in the left tibia of a 57 year old man.

phatase always is elevated in prostatic carcinoma and never in Paget's disease. There has been speculation as to why monophasic Paget's disease is rather common in the skull and humerus but practically unknown in the pelvis, femur and tibia. A suggested explanation is that the stimulus of weight bearing causes prompt and complete ossification of bone in Paget's disease of the pelvis and the lower extremities.

Long bones—In the humerus, Paget's disease frequently is partly lytic and partly plastic; in the femur and tibia, it follows the general pattern seen in the pelvis. Occasionally, in a bone such as the clavicle, there may be uniform sclerosis or eburnation of the sort seen in osteopetrosis or in some cases of Paget's disease of the spine.

Spine—Most cases of Paget's disease of the spine involve several segments and are accompanied by lesions in the pelvis, skull and lower extremities. One also sees coarse, interweaving trabeculae and an increase in the over-all size of the vertebral body. Occasionally, a vertebral body will be uniformly sclerosed or eburnated without any evidence of the usual coarse trabecular pattern. In such cases, a physician has greater confidence in his diagnosis if he is able to demonstrate typical lesions of Paget's disease elsewhere in the skeleton.

Progress of Disease

Paget's disease may remain confined to a single bone throughout the life of the patient; in such cases, diagnosis may be difficult or impossible without the aid of biopsy. Usually, however, other bones are or presently will be involved, and, fortunately for the radiologist, a case of Paget's disease that may be atypical in the spine or clavicle is apt to assume the conventional pattern in the skull and pelvis.

Complications

Fractures and pseudofractures—Straightforward pathologic fractures may occur in long bones weakened by Paget's disease, but they unite like any other fractures. Occasionally, one sees in the involved bones transverse slits or "cracks," which have been termed fractures or pseudofractures (figure 18). LeMay and Blunt[4] argue that the lesions in question are not fractures but rather are nutrient foramina which have become enlarged by engorged vessels beating against weakened bone. This contention seems to be supported by angiographic evidence.

Neoplasm—Neoplasms developed in three of Paget's five cases: in the left radius in case 1, in the right humerus in case 2, and in the calvaria in case 3. Some students of the disease believe that the incidence of neoplasm may be as high as 12 or even 15 per cent, but statistical proof is lacking, and certainly the picture is complicated by the fact that the development of a neoplasm presumably brings to light some cases of Paget's disease that otherwise might have been missed.

Arteriosclerosis and otosclerosis—Calcification of peripheral vessels and otosclerosis are fairly common complications of Paget's disease; but, as in the case of neoplasm, quantitative information on these conditions is lacking. Of course, the likelihood that deafness, arteriosclerosis or bone neoplasm will develop increases with age. However, even in the absence of rigorously controlled statistical analysis of data, there seems little reason to doubt that Paget's disease of the skull sometimes involves the middle ear, causing otosclerosis, that calcification of peripheral vessels is particularly frequent in Paget's disease, and that proneness to bone neoplasm is increased. On the other hand, ordinary otosclerosis is not Paget's disease localized in the middle ear, and, when old lesions of Paget's disease undergo sarcomatous degeneration, the resulting fibrosarcomas or osteosarcomas look and act like sarcomas arising in bone not affected by this disease.

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1. Shelmire, J. B., Jr.: A.M.A. Arch. Dermat. 78:191, August 1958.

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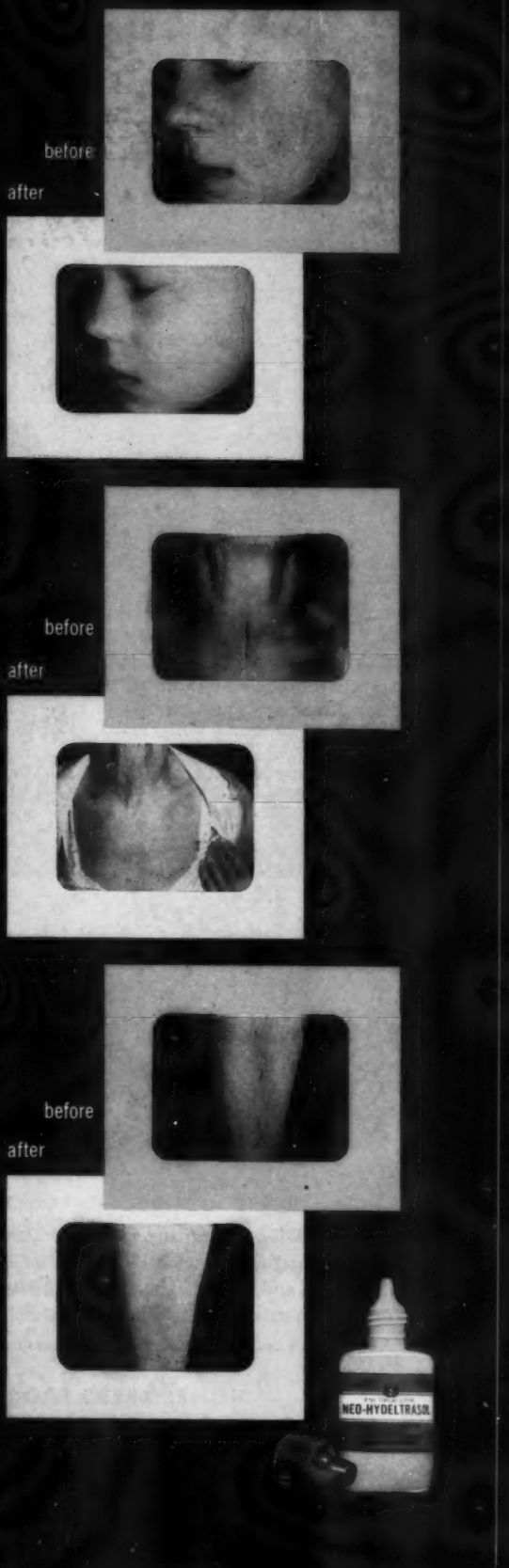

The Editor's Mail

After publication in January of the Postgraduate Medical Debate on "The Treatment of Rheumatoid Arthritis," the following letter was received. Dr. Robert C. Batterman and Dr. Paul O. Hagemann, participants in the debate, were invited to comment on Dr. Cohen's remarks. Dr. Hagemann declined comment, but Dr. Batterman has replied and his letter is also printed here.

TO THE EDITOR:

I have read with a great deal of interest the articles published in the POSTGRADUATE MEDICINE January 1959 issue under the heading of "Treatment of rheumatoid arthritis," by Drs. Batterman and Hagemann.

I cannot refrain from writing to express my displeasure in the conclusions reached by these authors. To read their statements would lead one to believe that we are still living in the 1920s as regards treatment of rheumatoid arthritis. I have been director of the Arthritis Clinic at the Philadelphia General Hospital since 1926, and ca state categorically that since the advent of cort sone and its derivatives, the disability from rheu matoid arthritis has greatly diminished. It is o interest that at the Philadelphia General Hos pital, in the presteroid period, we averaged 12 admissions with rheumatoid arthritis yearly however, in 1955 there were 18, and each suc ceeding year the number has likewise diminished.

We have advocated steroids over salicylates.

We have been users of gold almost since its advent in 1929. Only one out of three patients can truly expect to benefit from this substance, but only one of every two can tolerate it.

It is not factual any longer that diabetes mellitus is the direct result of the use of steroids.[1] Nor is it factual that duodenal ulcer may be produced by the administration of steroids;[2] elevation of blood pressure is a rare finding with the newer steroid derivatives; toxic psychoses do not exist except in the potentially psychotic individual; "absorption of skeletal areas such as the neck of the femur with telescoping of affected parts and resultant shortening and mechanical problems of weight bearing and walking" have never been encountered in the thousands of pa-

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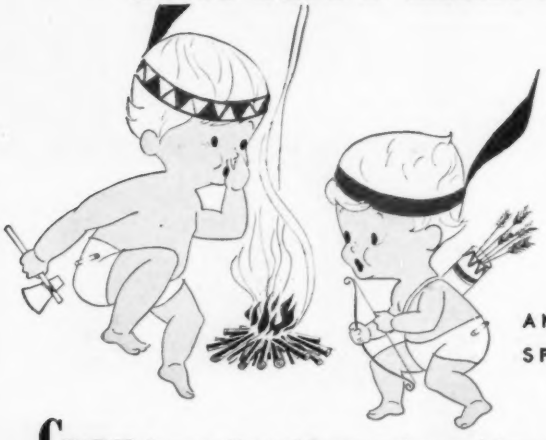

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tients treated by us; impairment of wound healing is no longer considered a problem; thrombopenic purpura has never been proved with steroid therapy; thrombotic purpura does occur, but all blood studies have been notoriously negative; the development of collagen disease is only a possibility when steroids are used injudiciously. In the case of #11, "severe electrolyte imbalance, shocklike state, and abstinence phenomena suggestive of addiction which might result from abrupt withdrawal of use" are only the result of improper reduction of dosage.

We go along with the possibility of adrenal insufficiency when steroids are used for long periods. This makes surgery dangerous; but awareness of such a state need not deter surgery.

We also concur with the development of osteoporosis, particularly in postmenopausal women. However, when one weighs the evidence of crippling against freedom from discomfort, it is difficult to argue the point.

Dr. Lawrence E. Meltzer and I have studied 80 cases of rheumatoid arthritis that have been treated with steroids for periods varying from 30 to 100 months, and while 100 per cent have evidenced moon face, an untoward reaction which is of little importance except for its cosmetic effect, osteoporosis did occur in approximately 13.75 per cent. This is a smaller percentage than has been reported by others. We still feel that steroids are a boon to the arthritic.

Very truly yours,
ABRAHAM COHEN, M.D.
Chief of Arthritis Clinic,
Philadelphia General Hospital

1. To be published.
2. MELTZER, L. E., BOCKMAN, A., KANENSON, W. L. and COHEN, A.: The incidence of peptic ulcer among patients on long-term prednisone therapy. Gastroenterology 35:4 (October) 1958.

TO THE EDITOR:

It is unfortunate that Dr. Cohen is displeased and perturbed by the recent articles by Dr. Hagemann and myself in POSTGRADUATE MEDICINE. Apparently, he has continued to use steroids since the advent of cortisone in 1949 and has, in turn, utilized each new one as a "boon" for the treatment of arthritis without considering the over-all problem. The fact that several new steroids are in current use should make one pause and evalu-

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ate the possibility that past experience with the previous preparations was not satisfactory. Each new steroid has been introduced as being more potent and more safe. However, it was only after several years of continuous use that each steroid was found wanting. Whether the most recent preparations will also fall into this category remains to be seen. Of course, eventually a steroid may be found that will do what Dr. Cohen expects, but this is still conjectural.

Let us examine the facts as they have accumulated since 1949. The same year that cortisone was introduced, the American Rheumatism Association adopted the Therapeutic Criteria for evaluating medications advocated for treating rheumatoid arthritis (J.A.M.A. 140:659 [June 25] 1949). According to these criteria, it was immediately recognized that cortisone was of limited value; the most that one could achieve was subjective improvement, usually in grades 2 and 3, but with adverse effects. Occasionally, one could obtain a grade 1 improvement, but the likelihood of complete remission was slim. In 1951, when I was chairman of the Committee for Therapeutic Criteria in Rheumatoid Arthritis, these facts were brought to the attention of members of the American Rheumatism Association at their annual meeting. Freyberg and associates (J.A.M.A. 147:1538 [December 15] 1951) stated as a conclusion, "Initially we were concerned chiefly with the questions: (1) Can cortisone be tolerated for long periods by patients with a chronic illness? (2) Will it be beneficial? Now, 18 months after extensive trials, we are more concerned with the question: Will treatment with cortisone be worthwhile for this patient?" The latter question in view of the newer steroids should read: "Will treatment with any steroid help this patient?"

In the eleventh Rheumatism Review (*Annals of Internal Medicine*, vol. 45, 1956), the editors sum up the situation as follows: ". . . these agents constitute the only rapidly acting therapeutic weapons which can suppress the signs and symptoms of rheumatoid arthritis in many cases. But they are needed in the management of a minority of patients. Candidates for their use must be carefully selected."

Bunim at the twenty-ninth annual Graduate Fortnight of the New York Academy of Medicine (Bull. New York Acad. Med. 33:461, 1957) reviewed the subject as follows: "But the disease process is not eradicated and, indeed, certain destructive lesions continue to progress even while

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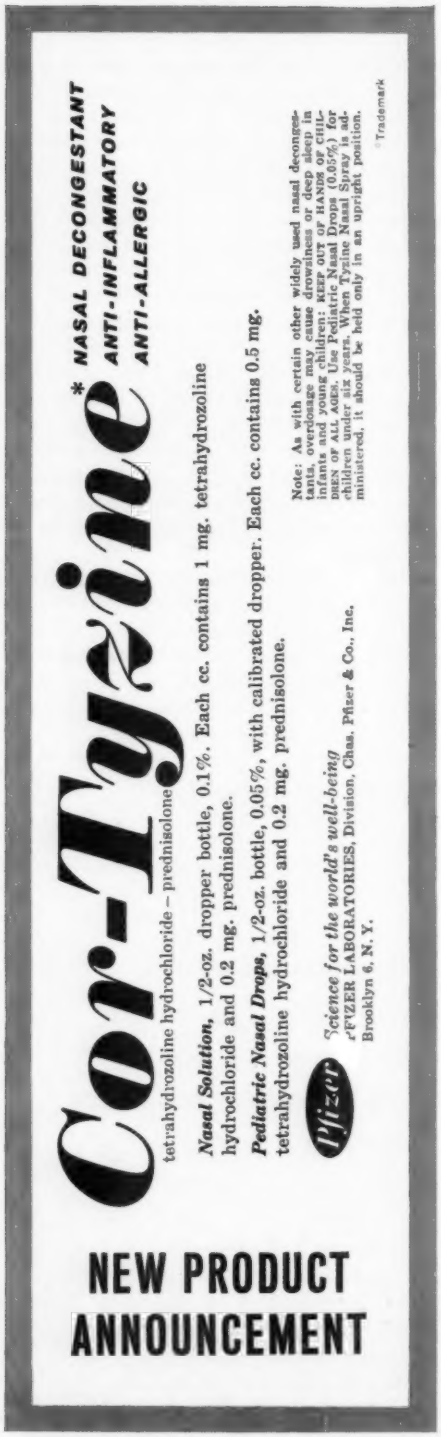
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adequate daily doses of steroid and apparen clinical improvement are maintained. The initia response to these agents in properly selecte cases is uniformly impressive, but in a consider able proportion of patients improvement decline as administration is prolonged beyond 6 to 1 months." Bunim emphasizes four major side ef fects noted with prolonged steroid administra tion: Peptic ulcer, osteoporosis and compresse fractures, mental disturbances and collagen-vas cular disease. He concludes that "Synthetic anti rheumatic steroids have certain advantages in contrast to cortisone and hydrocortisone but share with the latter important limitations and serious side effects, some of which may be fatal."

In 1957, Bunim and associates reviewed their experiences with several steroids, particularly with prednisone. They also summarized the literature pertaining to deaths related to steroid therapy. This review was part of a symposium on rheumatoid arthritis (J. Chron. Dis. 5:751, 1957), and was also presented at the ninth International Congress on Rheumatic Diseases at Toronto in June 1957. It is evident that "in contemplating institution of prolonged therapy in rheumatoid arthritis, or in any other disease, it is imperative that the physician carefully estimate the risks involved."

It is not necessary to belabor the point. With few exceptions, many eminent authorities have recognized the shortcomings of chronic steroid therapy. Favorable short-term therapy may be of benefit in certain arthritic conditions. Rheumatoid arthritis, because of its chronic nature, must be re-evaluated for the possible long-term effects of steroid therapy. To date, such therapy has proved in the main unsatisfactory and dangerous.

Evidence for the occurrence of the toxic manifestations noted in my review is so overwhelming that the statements of Dr. Cohen must be considered as the opinion of only one investigative group. To refer to his own work as "To be published" is not scientific rebuttal of an issue.

Since our articles dealt primarily with salicylates versus steroids, there is no point at this time in discussing gold therapy. Suffice it to say that since many rheumatologists have found steroid therapy unsuccessful, gold therapy is again rising in importance as the method of choice. Recent reports and exhibits at both the American Rheumatism and American Medical Associations attest to the efficacy and relative safety of this form of treatment.

ROBERT C. BATTERMAN, M.D.

"There is some evidence that triamcinolone is more effective at a smaller dosage than are other steroids in controlling both the skin and joint lesions in psoriasis, whether or not complicated by arthropathy."

"Triamcinolone appears to compare favorably with other steroids for use in those situations in which edema and sodium retention have been complicating problems."

"It [triamcinolone] may also be the steroid of choice for patients in whom psychic stimulation, euphoria, voracious appetite, and weight gain should be avoided."

"... the drug [triamcinolone] does produce the other side effects and untoward reactions common to the glucocorticoids. At therapeutically equivalent doses, the frequency and severity of clinical manifestations of hyperadrenalism — rounding of the face, fat deposition, and hirsutism — are essentially the same. Likewise, there is little indication that the relative incidence of osteoporosis is materially decreased after the long-term use of the drug."

"Triamcinolone apparently does not cause the euphoria sometimes seen with other steroids, and the occurrence of mental depressions is uncommon."

"Current evidence suggests that the drug [triamcinolone] may not produce as high an incidence of peptic ulcer as do other steroids."

"Cutaneous erythema seems to be a side effect peculiar to triamcinolone."

"The usual contraindications and precautions of glucocorticoid therapy should be followed in the use of triamcinolone, keeping in mind that prolonged therapy with this drug will suppress the function of the patient's own adrenals by interfering with the pituitary-adrenal axis."

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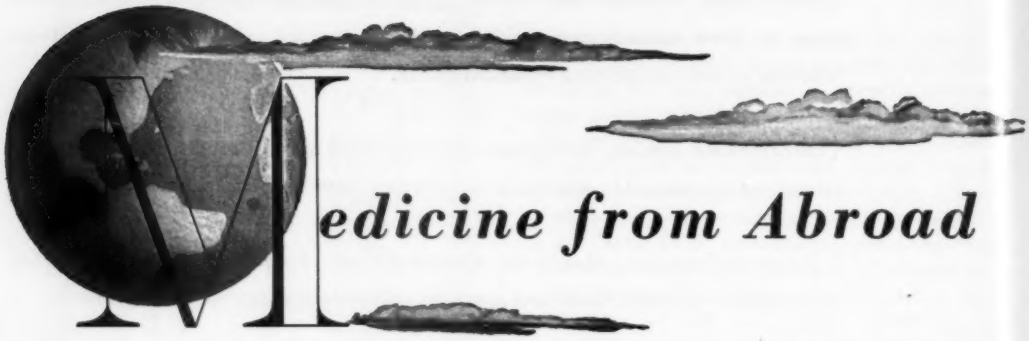

Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Lung cancer—In the *Medical Journal of Australia,* Dr. H. Maynard Rennie of Sydney has discussed problems of lung cancer from a physician's viewpoint. He stated that for all practical purposes the only curative treatment is surgical resection of the affected lobe, with or without removal of the mediastinal glands. Irradiation is chiefly palliative, alleviating mediastinal pressure effects on the superior vena cava or esophagus, pain due to secondary deposits in bone, cerebral metastases, severe cough and uncontrollable hemoptysis. Occasionally, however, irradiation will effect a cure.

In summary, he offered the following recommendations:

1. Preventive measures. Those who wish to smoke should never have more than 15 cigarettes a day. Sources of atmospheric pollution by potential carcinogenic agents should be eliminated.

2. Early diagnosis. All heavy smokers (both men and women) of cigarettes (20 or more per day) should have an x-ray examination of the chest every six months, and the films should be made available for comparison. If any suspicious lesion is found, the patient should be referred promptly to his medical advisor, and receive an immediate and full investigation by a trained thoracic team.

3. Early treatment. The thoracic surgeon should be given an early opportunity to explore the chest. Often this should be done before a definite diagnosis is made, for at least eight out of 10 patients submitted to thoracotomy on the suspicion of the diagnosis will be found to have malignant disease, and the opportunity for cure is then immediately at hand.

Gastroscopy—In the same journal, Dr. W. E. King of Melbourne has reviewed 1100 cases in which gastroscopy had been performed.

According to Dr. King, three main reasons for looking at a chronic ulcer are:

1. To determine whether or not the ulcer is malignant. The site of the ulcer may be an indication, as those on the greater curvature are nearly always malignant; however, the ulcer on the lesser curvature sometimes presents a very real problem. The size of the ulcer on x-ray examination is not helpful in making a decision.

2. To assess healing. This can be done only by gastroscopy, as clinical features are not reliable, and x-ray examination is not particularly useful.

3. To avoid false diagnosis. Sometimes an ulcer is diagnosed on barium meal x-ray examination, and yet gastroscopy shows the lesion to be an irregularity in the mucosal folds holding up the barium. Gastric diverticula (only two cases have been seen) may be another source of error. In such cases, the smooth opening of the sac is obvious to the gastroscopist.

In hematemesis and melena, gastroscopy in properly selected cases may provide much useful information. It cannot be performed during active bleeding, but can be easily carried out immediately after bleeding has ceased. During 1953 and 1954, gastroscopy was performed on 55 such patients as a definite trial procedure. In 28 patients, acute or chronic ulcers were found.

(Continued on page A-104)

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angina attacks

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Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

References:

1. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology 8:504, Dec. 1957.
2. Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.
3. Eskwith, I. S.: The holistic approach to angina pectoris. Am. Heart J. 55:621, April 1958.

WALLACE LABORATORIES, *New Brunswick, N. J.*

*TRADE-MARK CML-7013-19

AUSTRIA

Essential arterial hypertension—In a lecture delivered before an assembly of Austrian physicians, Dr. E. F. Hueber described the pathogenesis of essential arterial hypertension and discussed some of the problems of treatment, with emphasis on indications for drug therapy.

Using his own published observations, Dr. Hueber stressed the need for early recognition of hypertensive disease. Treatment necessitates long periods of preliminary observation and accuracy of control. Since blood pressure fluctuates spontaneously, natural phases of lower or normal pressure readings may be erroneously attributed to therapy. In many patients, pressure may be maintained at normal levels by relaxation therapy alone. Drug therapy should be initiated only when other therapeutic trials have been unsuccessful; it is usually recommended for patients whose pressure readings are more than 200 mm. of Hg systolic and 120 mm. diastolic.

When relaxation therapy results in significant reductions of blood pressure, these results can be further improved by drug therapy. In hospitalized patients, the combinations of protoveratrine with reserpine and of *Rauwolfia* with HYDERGINE® will give superior results. *Rauwolfia* combined with pentapyrrolidinium, which reduces blood pressure significantly, is excellent for prolonged therapy for outpatients, and preliminary trial results of long-term treatment with the combined use of reserpine and CHLOTRIDE® were very favorable. Chlotride effects a drop in blood pressure by means of increased diuresis and elimination of salt; this drop is more pronounced when the drug is administered with reserpine.

Dr. Hueber added that, in the past 25 years, treatment with a salt-free diet had achieved best results when the diet was rigidly maintained. With Chlotride, the patient can be less rigorously restricted in his intake of salt during the period of initial salt withdrawal. In conclusion, Dr. Hueber suggested that care be taken in telling certain patients the outcome of blood pressure tests; otherwise, a neurosis may develop in addition to their hypertension.

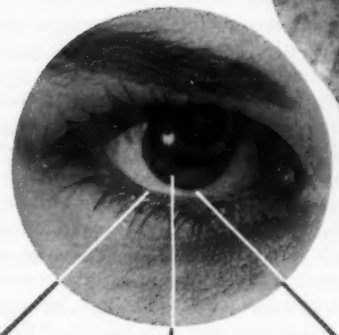
Ureteral stenosis due to endometriosis—The chief discussion at the meeting of the Austrian Society for Urology was presented by P. Deuticke, who reported on a case of juxtavesical stenosis of the ureter caused by endometriosis. The patient was a 45 year old woman who had borne one child and had never had a gynecologic operation. She complained of pain of several months' duration in the area of the right kidney. The urine was normal and the bladder appeared to be normal. Repeated intravenous pyelography revealed a progressive, ultimately grave hydronephrosis and a stasis dilatation of the entire ureter immediately up to the urinary bladder. This evidently indicated the presence of stenosis in the intramural portion of the ureter, although the ureteral catheter could be easily introduced.

Intravaginal examination in the region of the distal portion of the ureter revealed a small, hard, only slightly mobile tumor as large as a cherry stone in the anterior vaginal fornix. Otherwise, the uterus and the adnexa were normal, and even curettage and cervical biopsy showed normal conditions of the tissues. Surgical exposure of the urinary bladder revealed the corresponding tumor in the wall of the bladder. The distended ureter was severed exactly before the point of its entrance into the bladder; the tumor, together with the intramural ureter in its center, was excised. The defect in the bladder was closed, and, with the aid of drainage by means of a plastic tube in the upper end of the suture of the bladder, the proximal portion of the ureter was freshly reimplanted by joining mucous membrane to mucous membrane. Healing was uneventful.

Histologic examination showed focal endometriosis in the wall of the urinary bladder and the adventitia of the ureter; the wall of the ureter itself remained unaffected. After the operation, the hydronephrosis disappeared. Due to slight general complaints, nine months after this operation the woman was castrated by x-ray. Subsequent re-examination 35 months after this operation showed that the urine was clear and the bladder was normal. Both kidneys exhibited normal anatomy and function, and the patient no longer complained of pain.

In the course of the discussion, R. Blum mentioned another case of endometriosis of the urinary bladder which also had resulted in stricture of the ureteral orifice. In this case, cure was effected by resection and reimplantation of the ureters. The patient had had two previous gynecologic interventions: excision of a myoma 11 years before and interposition of the uterus six years before. The histologic examination proved the presence of a silk thread in the area of the endometrial glands and cellular elements; thus, the examination proved that the endometriosis was spread directly by the operation.

(Continued on page A-106)



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llergic conjunctivitis,
piscleritis)

inflammatory
(acute catarrhal conjunctivitis, ulceration, meibomitis, keratitis)

traumatic
(foreign bodies, burns, abrasions, lacerations)

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R. Ulm reported that in the last few years seven patients with endometriosis were treated at the First Gynecological Clinic of Vienna University. All the nodules caused by endometriosis developed extraperitoneally in the space between the cervix and the bladder, and they grew to various depths in the posterior urinary bladder wall. Since in all seven women the anterior cervical wall was surgically split, we may well assume a causal relationship between the operative intervention and the subsequent hyperplasia endometrii. This suggested relationship became more apparent when the histologic examination made it possible to pursue a continuous infiltrative growth of the endometrial glands of the anterior wall of the uterine cervix into the posterior wall of the urinary bladder.

Since all the women were still in the middle age of their sexually mature period, paradoxical hormonal therapy or irradiation for castration was out of the question. Yet the pain of these women, which became almost unbearable during the premenstrual time, demanded prompt treatment. Professor Antoine excised the endometrial tumor in every case. Only once were the endometrial changes right at the orifice of the ureter, and there were no indications of ureteral stenosis. The operations were performed 8 to 11 years ago; since then all the patients have remained symptom-free, and two women have given birth to healthy children.

BRAZIL

Turbidity and flocculation tests—According to José Fernandes Pontes, Dirceu P. Neves, Sharif T. Kurban, Arnaldo de Godoy and Luiz Caetano da Silva, understanding of the physicochemical and biologic mechanisms regulating flocculation and turbidity tests is of fundamental importance in evaluating their results. Gamma globulins are the main factor responsible for precipitation in the studies, and the variable interference of other factors accounts for the behavior of the tests in different hepatobiliary diseases.

Most useful for differential diagnosis of jaundice and acute hepatitis are turbidity and thymol flocculation, cephalin-cholesterol flocculation and zinc sulfate turbidity tests.

The thymol turbidity test may show very high values, sometimes higher than those of the zinc sulfate turbidity test, in viral hepatitis; this fact may be observed in some cases of obstructive jaundice.

The zinc sulfate turbidity and the thymol flocculation tests are the last precipitation tests to yield positive results in cases of long-standing obstructive jaundice. These tests may also remain positive for many months after the acute phase of viral hepatitis and, therefore, they are not useful as criteria of healing. Generally, the first test to become negative in the evolution of viral hepatitis is the cephalin-cholesterol flocculation test, followed by the Lugol precipitation test.

High values of the Lugol test point to a great alteration in the albumin fraction or in the albumin-globulin ratio. This test indicates severe liver cell injury and is helpful in differentiating between acute hepatitis and cirrhosis and in the transition of hepatitis into cirrhosis. The results of this test when compared with those of ammonium sulfate and zinc sulfate turbidity tests have, in some instances, proved to be more reliable. It has also been used in searching for the cause of gastrointestinal hemorrhage.

The zinc sulfate and the ammonium sulfate turbidity tests are most useful in chronic hepatic diseases because they indicate more accurately the serum gammaglobulinemia.

The Weltmann reaction may be important in some instances. In hypergammaglobulinemia of hepatic origin, such as in cirrhosis or hepatitis and in the later or infected stages of biliary obstruction, the coagulation band is widened; in acute infected cholestasis or in neoplastic conditions it may be shortened (shifted to the left).

ENGLAND

Hospital sterilization—A conference on this important subject, held at Southampton University, was attended by more than 300 representatives of medical, nursing, engineering and administrative staffs of hospitals and of hospital management committees. Brigadier J. D. Welch gave an account of the first phase of the investigation of sterilization in hospitals that is being carried out under the auspices of the Nuffield Provincial Hospitals Trust. So far only the first phase has been completed, which was a study of present methods of sterilizing in

six typical hospitals: a London teaching hospital, three large provincial general hospitals, and two "cottage" (rural) hospitals. The results of this study disclosed a disturbing situation. Many of the methods used to time the boiling of instruments were haphazard. Swabbings showed that 18 per cent of all ward equipment and 12 per cent of all theater equipment were contaminated. Autoclave departments were singled out for particularly heavy attack; much of the unsatisfactory state of affairs was due to the lack of training of autoclave operators, who were usually porters with other hospital jobs.

Dr. C. A. Wells, professor of surgery at Liverpool University, said that in the last few years surgeons had allowed themselves to become too complacent about postoperative sepsis. In any outbreak of sepsis, responsibility should rest squarely on the surgeons, whom bacteriologists have lulled into a false sense of security.

Dr. E. M. Darmady, senior pathologist of the Portsmouth pathologic service, described the control and supervision of hospital sterilization in his area. A team consisting of a doctor, a bacteriologist and a senior bacteriologic technician carried out, under Dr. Darmady's supervision, a survey similar to the Nuffield investigation. This team focused their attention on ward sterilization technics and the conditions under which nursing staffs were expected to perform sterilizing and dressing duties. These conditions were found to be both unfair to the nurses and dangerous.

The proper cleaning of instruments by scrubbing them with soap and water before sterilization was found to be important.

Value of vitamins—In the *Practitioner*, Dr. A. H. Douthwaite, the well-known physician and pharmacologist, summed up an interesting group of articles on vitamins by discussing the use and abuse of multivitamin preparations. He suggested that the time had come for discarding the term "vitamins," for, while they may be vital in some sense, they are certainly not amines. Since the nature of the chemical substances of these preparations is now known, they should rightly be regarded as food factors, or sometimes as drugs, and treated with scientific respect.

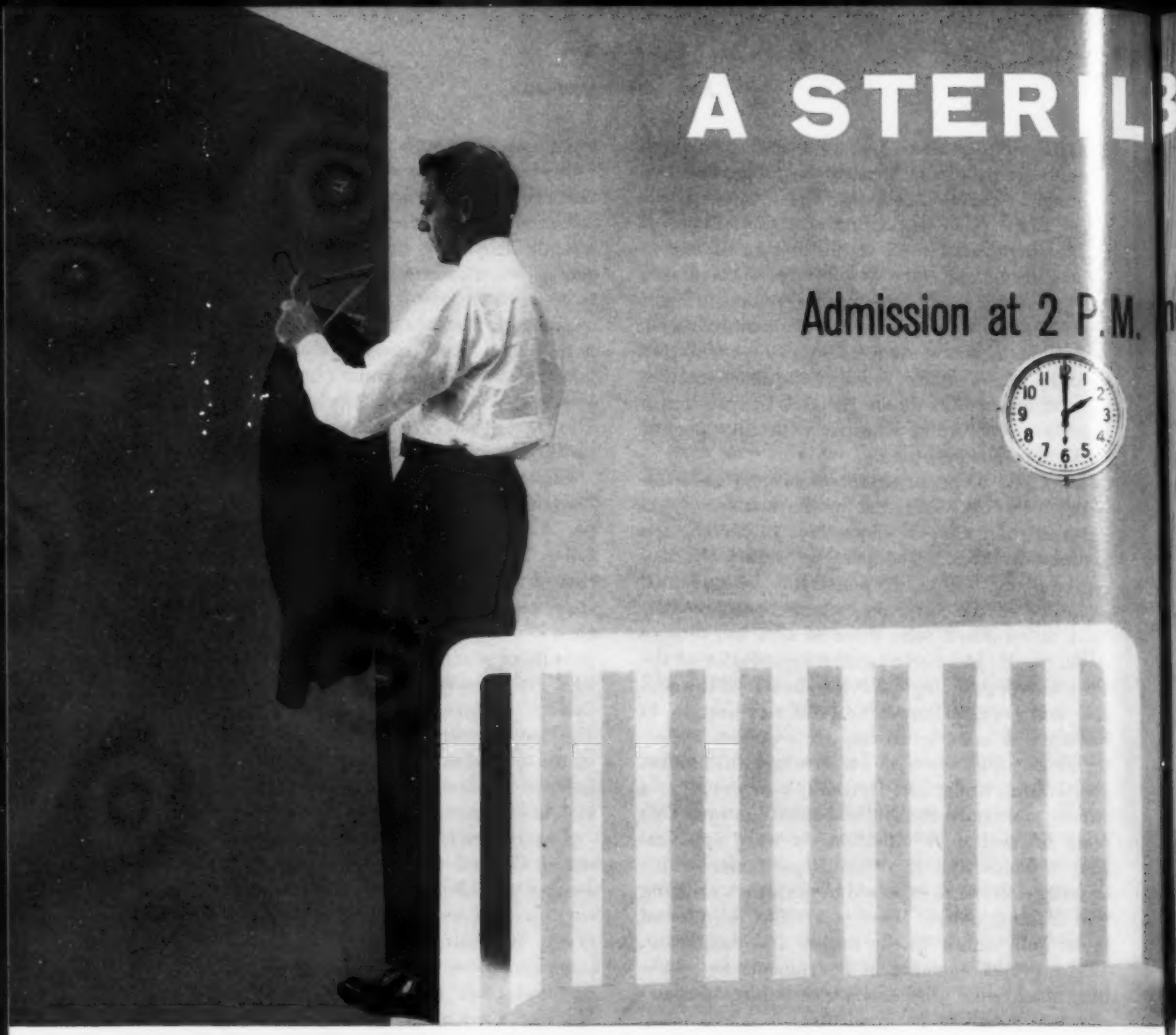
The main indications for the administration of multivitamin preparations, most of which contain at least vitamins A, B, C and D, are lack of adequate intake and imperfect absorption; in terms of disease, this may be stated as inanition, repeated vomiting, fad dieting and chronic diarrhea such as is sometimes encountered as part of the postgastrectomy syndrome and as the state following extensive resection of the small intestine. The faddist who believes that health can be achieved only by dietetic means quite often has vitamin-deficiency diseases, and may be persuaded to take multivitamin preparations. Protracted vomiting of pregnancy may lead to an appreciable vitamin deficiency that may adversely affect the fetus as well as the mother. If multivitamin preparations cannot be retained, and this is rare, at least the readily depleted and therefore most frequently lacking vitamins B and C can be administered by injection.

Chronic diarrhea requiring supplementation of vitamins in the diet is present in ulcerative colitis, idiopathic steatorrhea and intestinal "hurry" following gastrectomy, and after extensive resection of the ileum for Crohn's disease. Quite apart from frank illness with signs of multiple deficiency, some degree of vitamin deficit may arise in spite of a normally adequate diet in the young who are growing rapidly, in pregnant women, and in patients with prolonged pyrexial illness. The use of multivitamin preparations is justified in the instances cited until the cause of the deficiency has been eliminated and the evidence of deficiency removed.

Treatment of asthma—The Medical Research Council subcommittee on clinical trials in asthma in 1956 found no real advantage in cortisone acetate as compared with bronchodilator drugs in treating chronic asthma. This result surprised those whose experience indicated that corticosteroids are often of great value. Dr. H. Morrow Brown, consultant chest physician at Derby, has accordingly carried out another trial using prednisolone in 90 patients who have chronic asthma, and has reported his results in the *Lancet*. Except when bronchospasm was very severe, the dosage given was 5 mg. three times daily for a week, followed by reassessment and adjustment of the dose. Only patients in whom bronchodilator drugs had failed to produce a satisfactory response were included.

Large numbers of eosinophil leukocytes can be found in the sputum of asthmatic patients, but so far these findings have had no bearing on treatment. Corticosteroids clear the blood of eosinophils, but it was soon found that they did not clear the sputum. Even more interesting was the indication that eosinophils in large numbers in the sputum were associated with a good response to prednisolone, and few or no eosino-

(Continued on page A-110)



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1. Poth, E. J.: Intestinal Antisepsis in Surgery, J.A.M.A. 153:1516, Dec. 26, 19

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phils with a poor response. Experience showed that if patients with nonpurulent sputum did not improve after receiving 15 or 20 mg. of prednisolone per day for two weeks, continuing treatment would provide no significant benefit. In children, only the very worst cases were treated, and then only after the demonstration of eosinophils in the sputum had put therapy on a sounder basis. Dr. Brown's observations so far suggest that recurrent bronchitis or frequent colds in children should be suspected of having an allergic basis, and that examination of sputum may often give a true diagnosis.

The results of the clinical trial indicate that prednisolone is very useful in treating chronic asthma if the sputum contains large numbers of eosinophils. In the absence of an eosinophilic sputum, a satisfactory response is unlikely, and prednisolone is contraindicated. Only the smallest possible effective dose was administered, so that side effects and complications were less likely to occur. The most serious complication was glycosuria, of which there were three instances, one in a patient with mild diabetes.

FRANCE

Cancer in military personnel—Dr. H. Hébrard, chief of the Center of Military Cancerology, has reported on the incidence of cancer in persons of military age. Since military personnel often received treatment in civilian hospitals, his statistics are incomplete, but he was able to assemble data on 2700 cases of malignancy occurring during the period 1942 to 1957. Two hundred and seventeen of the patients were between 20 and 25 years old. Although only a small proportion of army personnel was in the upper age bracket, the incidence of cancer in the patients studied rose until age 45, when it dropped sharply as older men left the service.

Hébrard's research included tumors of all organs, beginning with a report of 206 cases of tumors of the testes and including sarcomas of bone and connective tissue and Hodgkin's disease. Skin tumors, such as epitheliomas and nevocarcinomas, were relatively rare; breast tumors were proportionately common. A few patients had cancer of the digestive tract, stomach or rectum, and Hébrard believes that we cannot rely on the patient's age in excluding such a diagnosis, especially in cases where unquestionable symptoms are present. Cancer of the nasopharynx occurred occasionally.

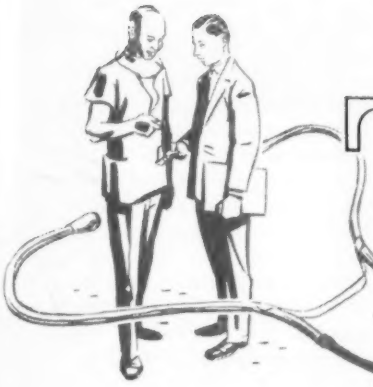
Sarcoma was relatively common in men less than 35 years old. Hébrard determined the ratio of sarcoma to epithelioma to be 55 per cent in persons less than 25 years old, 25 per cent in those aged 25 to 35 years, and not more than 10 per cent in persons more than 35 years old.

Based strictly on five year survivals, the course of the malignant tumors did not appear to be related to the patient's age; the prognosis depended on the tumor's histologic character. Dysembryomas in the testes grew rapidly in men less than 25 years old; but seminomas, generally seen in somewhat older men, had a good prognosis. Reticulum cell sarcoma in young people spread over the entire body in a few months. Epitheliomas of the skin and lips recurred most often and progressed most rapidly in young patients; therefore, they should have frequent checkups. In Hodgkin's disease, the prognosis was not related to the patient's age.

Although trauma is undeniably a causative factor in cancer, in this investigation malignancy following trauma was relatively rare in proportion to the enormous number of injuries occurring in military life. Such cancers, however, were of considerable medicolegal interest. In nine patients, cancer occurred at the site of old wounds caused by shell fragments or as a result of accidents or minimal lesions from work. The latency period varied between 10 and 60 years, and the patients' ages between 45 and 76 years. In nine patients, cancer developed three months to two years after a fresh wound or after injuries by barbed wire, plant thorns or bruising. Two of the 20 sarcomas occurred following wounds caused by shell fragments and by an automobile accident; four of the 20 breast cancers also followed injury.

The incidence of cancer of the alimentary tract was two or three times higher in former prisoners of war than in others of the same age group, but the course of the disease followed the usual pattern. Alimentary tract cancers occurred more frequently in the malnourished civilian population during the period of the German occupation.

Hébrard also found that tropical climates aggravated the spread of cancer in Europeans, and that sun stimulated the development of skin tumors.



Through the Stethoscope

WENDELL J. S. KRIEG

Letters to a Medical Student

My dear son:

Your question as to whether your research should be basic or clinical is best answered by a consideration of your own temperament. Ordinarily, perfectionists and introverts like you are happier with fundamental research, because the conditions can be better controlled. As you say, much clinical research could be "chucked out the window." That is more appropriate to the older work, before the insistence on scientific method. The human organism is a tremendously complex microcosm, much more so than a monkey, because we have a psyche which reacts on our soma, and we are being studied by one of our own species. Clinicians often do not understand why basic scientists do not take over research problems on clinical material, and it is well to have an answer ready.

Unless clinical research meets the fundamental requirements of scientific method, the results of labor on it, too, will be chucked out the window by future workers. The careful investigator does not want that to happen with his work. He has only his work to invest; he cannot turn to medical practice. He wants to do as good a job as he can on the subjects which he is interested in studying. When you see a laboratory man shying from a clinical problem, there is a reason. He may feel uneasy at the lack of controls; he may feel frustrated that no experiment can be designed and that he must take natural cataclysms for his material. He may feel he could never get proper fixation of tissue or attendant data or history. Usually, he feels he hasn't the fundamental knowledge he needs to attack the problem. So over and again he is thrown back to the laboratory and the microscope, where he can control conditions and study what he needs to know.

You can, with standardized technics in an hour's work, lop off the frontal lobe from the brain and sever a billion neurons from their connections, but it may take 10 years to find out just what you have done. And, paradoxically, the full answer will not come from any study of the brain you have damaged but partly from those of rats and monkeys.

Men who study in the fundamental sciences have this quirk in their natures. They are not disappointed medical students or men who wouldn't know what to do with $20,000

(Continued on page A-116)

a year. Rather, they are men who, unfortunately for their serenity, would rather find the real answers than do anything else in the world, and they know what they have to sacrifice to find them. They have their life invested in these things, but they must be interested—spontaneously interested—and they are awfully hard to be dragged or drugged.

Practitioners do not have time for these things, but it is because of a standard they have set for themselves, and it is largely an economic one. The successful physician, it seems, is just the one who can best afford to devote much of his time to research, for he can always come back, always quickly recoup.

Presuming I have given you enough reasons for doing your work at all, I should now like to mention a few thoughts about how to do your work efficiently and happily.

In the first place, you can be happier at your work and will do more of it if you love it. Love of the work may not be necessary for some kinds of livelihoods, but it is absolutely necessary for the professor, researcher and creative worker generally. There is no point whatever in going into such work unless you would feel unhappy if you did not. In fact, with the present economic opportunities for anyone of ability and good background, I would say that you pay a great price for this career, so you must enjoy it. If you ever come not to love it, get out of it by either taking up academic administration or entering business or practice.

However, one can let love of one's work be a weakness and constantly use it as a refuge and a means of simplifying the problems of life. You can get into this vicious circle with fatal facility, imagining that whenever you are working you are doing the proper thing, and you use this as an excuse for never doing anything else. Then your family protects you because you are working, and so your problems become even simpler. It works beautifully and you continue it. More work means more publications; more publications mean more honor; more honor promises more money. You are a "sacred cow," and nearly literally, for you are standing in a stall and giving milk. Basking in this incubator existence, you feel comfortable and undistressed, and you retreat more and more

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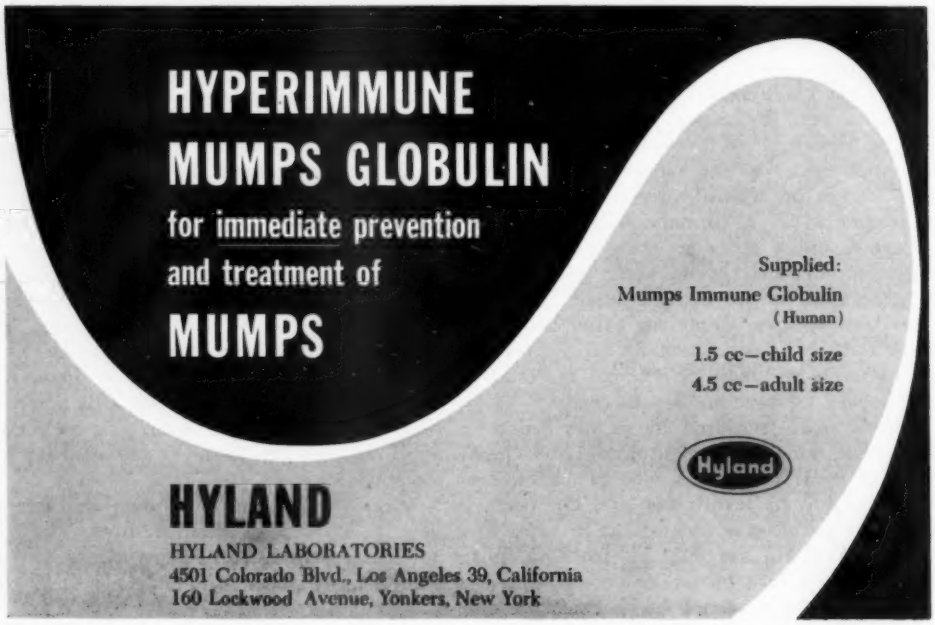
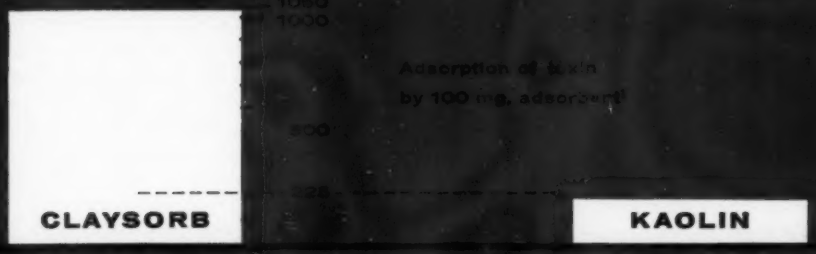


in diarrhea . . .

adsorptive power



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1. Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) *46*:493 (Aug.) 1957. 2. Barr, M., and Arnista, E.S.: *Ibid.* *46*:486 (Aug.) 1957. 3. Barr, M.: *Ibid.* *46*:490 (Aug.) 1957.

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from other interests and problems. A well-known experimenter signs his salary checks over to his wife, who buys his socks and suits. If surprised with a luncheon guest, he has to borrow a dollar. These anecdotes are often regarded as quaint and lovable, but I hope no one ever can tell such of me. I want to go on selecting my own neckties. I wouldn't want the feeling at 65 of waking up to the distorted life I had led and what I had missed.

I have always felt that the professor's security is enervating, although I believe it is fruitful and necessary. It can undermine his character, his resourcefulness and his contact with life, which finally can react even on his work by making him effete. We should feel an obligation to force ourselves out into the world, not just the scientific world, and to do something really on our own: build a house, cruise singlehandedly along the coast of Maine, make a social success somewhere we are unknown. These occupations rotund one's nature and make a professor more fitted for instructing progressive and virile young men.

The medical sciences today are such fascinating and such rewarding fields that it is difficult not to permit the circle of interests related to one's main subject to absorb lif so completely that one rarely finds energ or occasion for any interests or activities no connected with medicine. The net result is that one becomes a highly skilled technicia in a very exacting subject, but one is still technician.

The medical practitioner or researcher can obtain a lifetime of absorption and satisfaction in pursuing his work. The general public has an intense interest not only in the dramatic aspect of medicine but also in its progress; newspapers and popular magazines feature medical news and scientific reports, even before the doctor hears of them. The titles of fund-raising campaigns form practically a nosology, at least in neurologic lines. One might think the schools and colleges would give some instruction on these lines if only for its cultural value. But what does the biology student study—earthworms, bryophytes, *Amphioxus*—anything but man!

I will close then with a paradox. Perhaps this will all be changed in your day. I was born too soon!

And so, good night,
Father

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Information relating ECHO virus infections and human illness is being rapidly accumulated. To date, 20 antigenically different types of ECHO viruses have been established according to their ability to reproduce type-specific neutralizing antibodies. ECHO viruses have been recovered from humans with diarrhea, meningitis, meningo-encephalitis, summer rash and respiratory infections. The spectra of illnesses caused by ECHO viruses may not be fully known for many years.

Infection With ECHO Viruses and Observed Illnesses in Human Beings

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In recent years, many new viruses have been isolated in tissue culture from the alimentary tracts of human beings (predominantly children). Initially, many such viruses were discovered during poliomyelitis studies. Because of their nuisance value to such investigations and because their relation to human illness was not known or fully appreciated, these agents were referred to as orphan viruses.

The need for an antigenic classification of these newly recovered agents was recognized as a step in determining what role they play in human disease. In 1955, a committee[1] composed of interested investigators named these agents the enteric cytopathogenic human orphan (ECHO) viruses. The word human was used since similar viruses have been recovered from the alimentary tracts of other species of animals including cows, monkeys and swine. This committee found that these viruses share the following properties:

1. They are cytopathogenic for monkey and human cells in culture.
2. They are not neutralized by pools of the three types of poliomyelitis antiserum.
3. They are not neutralized by antiserums for Coxsackie viruses that are known to be cytopathogenic in tissue culture, and they fail to induce disease in infant mice.
4. They are not related to other groups of viruses recoverable from the alimentary tract (throat or intestine) by inoculation of primate tissue culture.

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TABLE 1

RELATION OF INFECTION WITH ECHO VIRUSES TO DISEASES IN HUMAN BEINGS

TYPE	PROTOTYPE STRAIN OR EPONYM	DISEASE IN PERSONS FROM WHOM VIRUS HAS BEEN ISOLATED	REFERENCES
1	Farouk	Aseptic meningitis	3
2	Cornelis	Aseptic meningitis	1, 2, 4, 5
3	Morrisey	Aseptic meningitis	1, 2
4	Pesacek	Aseptic meningitis; summer rash	1, 2, 6, 7
5	Noyce	Aseptic meningitis	1, 2
6	D'Amori	Aseptic meningitis; mild paralysis (?); rash	1, 2, 8, 9
7	Wallace	Aseptic meningitis	1
8	Bryson	Upper respiratory infection	10
9	Hill	Aseptic meningitis; summer rash	2, 11, 12, 13
10	Lang	Respiratory disease	2
11	Gregory		
12	Travis 2-85		
13	Hamphill 2-188		
14	Tow	Aseptic meningitis	2
15	Charleston 96-51		
16	Harrington	Aseptic meningitis; summer rash	2
17	CHHE-29		
18	Metcalf	Diarrhea	14, 15
19	Burke	Diarrhea	15
20	JV-1	Upper respiratory infection	10, 16

5. They are neutralized by human gamma globulin and by individual human serums.

The various ECHO types which have been designated are based on the ability of each virus to produce type-specific neutralizing antibodies. Thus far, 20 antigenically different types have been established by the committee.[1] Since the Coxsackie, poliomyelitis, and ECHO viruses all inhabit the human intestinal tract and share certain other properties, including production of disease in human hosts, these three groups of viruses are now regarded as members of a large family of agents which have been called the human enteroviruses.[2]

ECHO viruses have been recovered from human beings with illnesses including diarrhea, meningitis, meningo-encephalitis, summer rash and respiratory infection (table 1). In some instances, assembled data have suggested an etiologic association between infection with ECHO viruses and certain of these illnesses. The ECHO viruses have also been frequently recovered from the intestinal tracts of human beings who do not have any clinically observed illness.

To associate etiologically a new virus with human disease is often difficult. This is especially true if the illness is nondescript and mild without outstanding clinical features. The present report will bring together available information relating ECHO viruses with human disease. One must realize, however, that the clinical spectra of illnesses that are caused by these viruses may not be fully recognized for many years.

Aseptic Meningitis

It has been increasingly apparent in recent years that the three types of poliomyelitis virus are responsible for only a portion of the instances of aseptic meningitis that occur during the summer months. With precise diagnostic technics and detailed clinical and epidemiologic studies, certain Coxsackie and ECHO viruses have also been etiologically associated with this syndrome. Thus far, there is strong evidence that ECHO virus type 2,[4,5] type 3,[2] type 4,[6,7] type 5,[2] type 6,[8,9] type 9,[11,12] type 14,[2] and type 16[2] cause aseptic meningitis. ECHO virus type 1[3] and type 7[1] have been recovered from patients with this disease, but there is less evidence of etiologic association.

The syndrome of aseptic meningitis due to ECHO viruses is not clinically distinctive. Characteristically, fever, headache and signs of meningeal irritation are present. Gastroin-

testinal symptoms, lethargy, pharyngeal erythema and myalgia also may be present. A rash commonly may be present in cases of infection with ECHO virus type 9. In some cases, certain of these viruses may cause transitory muscular weakness and paralysis.[4,9] In these cases, the illness obviously is indistinguishable clinically from disease due to one of the poliomyelitis viruses.

The total leukocyte count usually is normal, but it occasionally is increased. There may be an increase in the percentage of neutrophils. Examination of the cerebrospinal fluid usually reveals an average leukocyte count of 200 per cubic millimeter, and the leukocytes are predominantly lymphocytes. The sugar content of the cerebrospinal fluid is normal and the concentration of protein is either normal or slightly increased.

The case history of a patient with aseptic meningitis due to ECHO virus type 9 will be presented.

Case 1—A seven year old boy was admitted to the University Hospital on August 28, 1957. He had been well until two days previously, when his neck had become stiff and headache and vomiting had occurred. On three occasions, his oral temperature had increased to 38.3° C. The past history was significant only in that the child had been immunized against poliomyelitis on three occasions.

Concurrently, a 10 year old brother of the patient had similar but less severe symptoms.

When the patient was admitted to the hospital, his temperature was 39.8° C. He appeared acutely ill, and examination revealed sinus tachycardia and nuchal rigidity. Kernig's sign and Brudzinski's sign were positive. There was moderate muscular tenderness in the calves, thighs and muscles of the forearm, but there was no demonstrable muscular weakness.

Routine urinalysis revealed that the urine was normal except for a positive reaction for acetone. The total leukocyte count was 9800 per cubic millimeter of blood, and a differential leukocyte count revealed 83 per cent neutrophils and 17 per cent lymphocytes. The erythrocyte sedimentation rate (Westergren method) was 44 mm. in one hour. Examination of the cerebrospinal fluid revealed an opening pressure of 200 mm. and a closing pressure of 140 mm. of cerebrospinal fluid. The leukocyte count of the cerebrospinal fluid was 1000 per cubic millimeter, and 50 per cent of the leukocytes were of the polymorphonuclear type. The total protein content of the cerebrospinal fluid was 63 mg. per 100 cc. and the value for the sugar was 48 mg. per 100 cc.

Cultures of the cerebrospinal fluid for bacteria and fungi did not yield any growth. Cultures of the throat, nose and stool were negative for bacterial pathogens. A heterophil test and serologic tests for syphilis, brucellosis and salmonellosis were negative. Specimens of serum obtained during the acute and convalescent phases of the illness were examined for antibodies against Eastern equine encephalitis, Western equine encephalitis, St. Louis equine encephalitis, lymphocytic choriomeningitis and mumps. The results did not indicate recent infection with any of the viruses responsible for these diseases.

The temperature became normal 24 hours after the patient was admitted to the hospital. The signs of meningeal irritation disappeared completely by the third day. The patient was dismissed on the sixth day, and he apparently was well. On the day after his dismissal, he was readmitted to the hospital because of anorexia, abdominal pain and vomiting. Physical and laboratory examination did not reveal any abnormality.

Special laboratory examinations—A virus was isolated from throat and stool washings on monkey-kidney-cell cultures. The agent thus isolated was shown by tissue culture neutralization tests to be ECHO virus type 9. Studies of serum obtained during acute and convalescent phases of the illness revealed a rise in antibodies during convalescence from the aseptic meningitis.

Respiratory Illness

ECHO virus type 20 (JV-1 virus) was recovered from infants in an orphanage, many of whom had a mild respiratory illness.[10,16] The illness was characterized by coryza, pharyngitis, and fever of short duration. Other manifestations included mild diarrhea, ery-

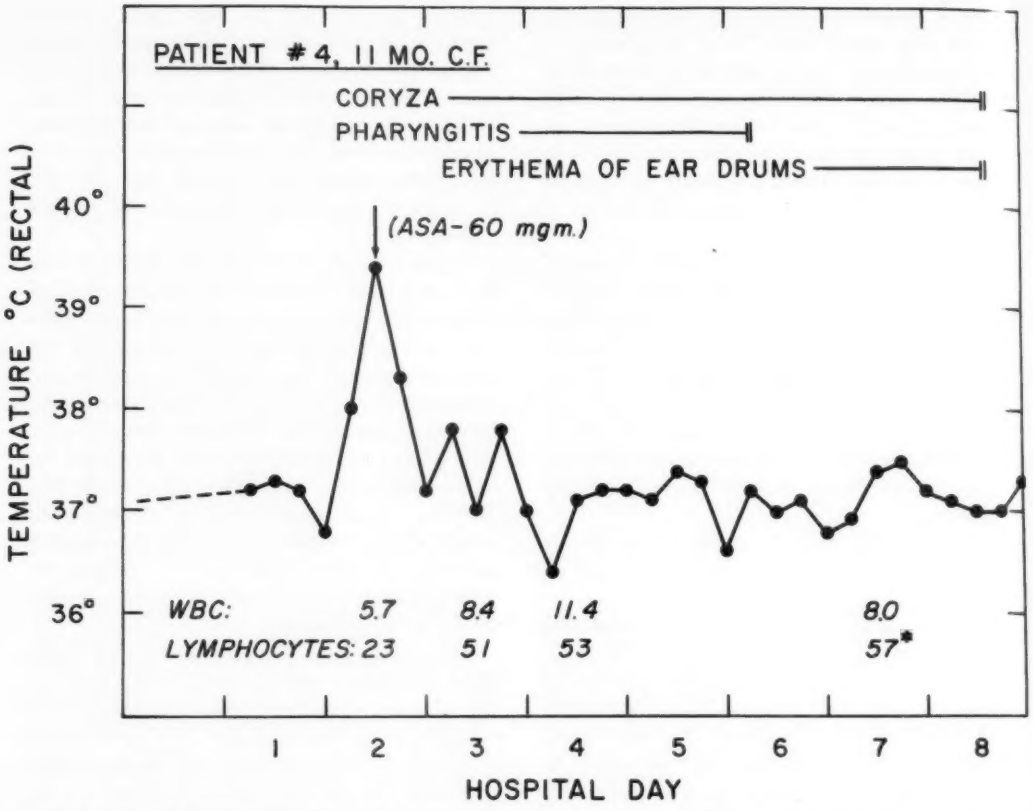

FIGURE 1. Graphic representation of clinical course of an illness caused by infection of an infant with ECHO virus type 20 (JV-1).

(From Cramblett, H. G., Rosen, L., Parrott, R. H., Bell, J. A., Huebner, R. J. and McCullough, N.B.: Respiratory illness in six infants infected with a newly recognized ECHO virus. Pediatrics 21:168 [February] 1958.)

thema of the ear drums and conjunctival congestion. The total leukocyte counts were not significant; differential counts revealed a predominance of lymphocytes. The illness observed in these infants closely resembled the common cold. A similar mild respiratory illness was observed in other infants from whom ECHO virus type 8 was recovered.[10] Figure 1 is a graphic representation of the clinical course of an illness caused by infection of an infant with ECHO virus type 20 (JV-1).

ECHO virus type 10 also has been recovered from children with respiratory disease as well as from chimpanzees with coryza. However, because of the large size of this virus, the distinctive cytopathogenic effects, and the existence of certain strains pathogenic for mice, consideration has been toward classifying it elsewhere.[2]

Exanthematous Illness

Certain ECHO viruses (types 4, 9 and 16) may cause illness in which the most prominent feature is a rash.[1,2,6,7,11,12] In many instances, the rash may be such as to be confused with exanthems, subitum, rubella or rubeola.

The clinical spectra of illness due to these viruses include any one or a combination of the following clinical features: minor undifferentiated disease, fever of unknown origin, a rash and aseptic meningitis. The appearance

of the rash is not diagnostic. It may resemble the rash observed in rubella, it may be morbilliform, or it may have a vesicular character similar to that seen occasionally in cases of infectious mononucleosis.

While most of the reported outbreaks of ECHO illnesses accompanied by a rash have occurred during the summer months, instances of such infections have been observed in the winter months.[17] The following case report is illustrative of an exanthematous illness with fever produced by ECHO virus type 9.

Case 2—A four year old child was seen in the Pediatric Clinic of the University Hospital on November 7, 1957. The child had had a fever as high as 39.4° C. for two days. The child also complained of sore throat and a "stomach ache." On the day before the child was seen in the Pediatric Clinic, a rash had appeared on the face and gradually had spread to the abdomen and extremities. Several children who attended kindergarten with the patient had had a febrile illness which had been associated with sore throat, headache and a similar rash.

The rectal temperature of the child was 39.7° C. The pulse rate was 110 and the respiratory rate was 20, per minute respectively. The child appeared to be acutely ill and complained of sore throat. There was a macular erythema with blotchy distribution over the cheeks. The rash was of a papular and vesiculopustular nature, and was surrounded by erythema in a few places on the arms and trunk. The tonsils were erythematous and congested, and two or three patches of white exudate were present in the crypts. There was a moderate posterior and posterolateral cervical lymphadenopathy, but there was no sign of meningeal involvement.

The total leukocyte count was 6800 per cubic millimeter of blood. The differential leukocyte count disclosed 46 per cent polymorphonuclear cells, 4 per cent eosinophils, 38 per cent lymphocytes and 12 per cent monocytes. The sedimentation rate of the erythrocytes (Westergren method) was 30 mm. in one hour. A throat culture for bacteria yielded normal flora.

The patient remained febrile for four days, and the rash also was present for four days.

Special viral studies—A virus was isolated on monkey-kidney-cell cultures of specimens obtained from the throat washings and stool of the patient. Examination of sera obtained during the acute and convalescent phases of the illness revealed a rise in the titer of antibodies against this virus from less than 1:4 to greater than 1:128. By means of tissue culture neutralization tests, the virus was identified as ECHO virus type 9.

Diarrhea

The causes of diarrhea in children are diverse. While some instances are clearly due to bacteria or fungi or are secondary to febrile illnesses unrelated to the gastrointestinal tract, the majority cannot be diagnosed by ordinary laboratory technics. It has been assumed that most of the latter infections are due to viruses.

Several of the ECHO viruses, including types 2, 6, 8, 10, 11, 12, 18 and 19, have been recovered from stools of infants and young children with diarrhea.[14,15] Mild diarrhea was observed in infants infected with ECHO virus type 20 (JV-1 virus), but the gastrointestinal symptoms were not as prominent as the respiratory signs and symptoms.[16] In the case of ECHO virus type 18, association between infection with the virus and the disease observed, i.e., diarrhea, has been established.[17] Evidence for association of the other ECHO infections with gastroenteritis is highly suggestive but not conclusive.

The illnesses observed in association with infections caused by ECHO virus type 18 were not severe. Diarrhea persisted for a mean duration of three days. Five or six large, watery, greenish stools usually were passed daily. They did not contain mucus or pus cells. Fever was not a prominent sign. None of the children was severely ill, and all recovered promptly with supportive therapy.

Minor Undifferentiated Febrile Illnesses

In all probability, certain of the nondescript febrile illnesses occurring in children during the summer are due to ECHO virus infections. This contention is supported by the recogni-

tion of such minor illnesses during epidemics of ECHO virus infections with more major manifestations.

Information relating ECHO virus infections and human illness is being obtained rapidly. Additional investigations will establish the potential importance of this large group of viruses in human illness.

ACKNOWLEDGMENT

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Symptoms of biliary tract disease are not always relieved after a primary operation. The incidence of overlooked common duct stones indicates the need for operative cholangiography at the time of primary biliary tract surgery. Nonsurgical disease also may cause a patient's symptoms. A complete survey of the entire gastrointestinal tract is mandatory to reduce the number of secondary operations.

Surgical Treatment of Persistent Symptoms Following Cholecystectomy

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It is always disturbing to a surgeon to find that symptoms may persist or recur following any surgical procedure, and this is even more distressing following such a common operation as cholecystectomy. A study of this problem is important to every physician, since surgery of the biliary system ranks among the four or five most frequently performed operations both in small community hospitals and in metropolitan centers. More such operations undoubtedly will be carried out as the age of patients concerned increases.

During the 11 year period from 1947 to 1958 more than 1600 patients underwent operation for biliary tract disease at the Ohio State University Hospital, 160 of them (one in 10) because of recurrent or persistent symptoms following a primary operation on the biliary tract (figure 1). Clearly the symptoms are not always relieved at the time of the first operation. It is our responsibility to improve this situation so that our recommendations for biliary surgery are not questioned by so many patients. Fortunately the number of physicians who share this pessimism toward gallbladder surgery is decreasing rapidly. The attitude of suspicion toward biliary tract surgery is a holdover from the days when cholecystectomy was done without sufficient investigation of the other possible causes for the patient's distress.

In recent years methods for accurate diagnosis of gallbladder disease have been available to every physician, but it must be remembered that the biliary tree is only a small branch of the gastrointestinal tract. Symptoms of disease of the biliary tract may overlap those of disease in other parts of the gastrointestinal system, and a complete survey of the entire system is mandatory before biliary surgery is recommended.

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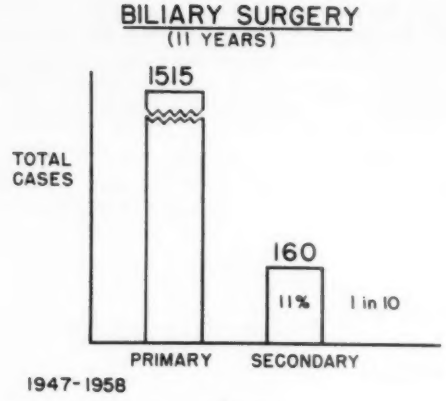


FIGURE 1. One in 10 biliary tract operations were of the secondary type.

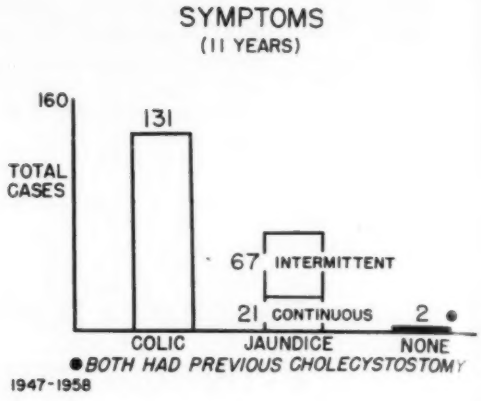


FIGURE 2. Three-fourths of the patients had recurrent biliary colic before secondary biliary surgery.

In older patients the incidence of associated pathologic conditions such as cancer and degenerative disease is greater. The constant threat of dual pathology makes it even more important to survey the entire patient before undertaking corrective surgery of a particular system.

Perhaps physicians should be more realistic in their preoperative discussions with patients. There is a tendency to promise too much following biliary surgery. Patients have great confidence in their "livers" and expect removal of the diseased gallbladder to obliterate all their complaints and effect a rejuvenation of general vigor. Cholecystectomy should never guarantee an unrestricted diet when turnips, cabbage and onions have been upsetting for years. It must be admitted that the best results follow in the case of a patient who has proved gallstones and attacks of biliary colic which have required the administration of narcotics for relief.

It is often difficult to ferret out the patient with persistent symptoms after cholecystectomy who might benefit by a secondary operation. In the majority of these instances at our institution, secondary operations have been limited to patients who have had recurrent biliary colic (81 per cent) or jaundice (42 per cent) (figure 2). In one-third of the cases of jaundice, it persisted from the time of the primary operation, and in two-thirds of the cases it was intermittent. Two patients who were entirely asymptomatic were operated on after an interval following cholecystostomy (figure 2).

Evaluation of Persistent or Recurrent Symptoms After Cholecystectomy

The symptoms presented by a patient who has had cholecystectomy previously may differ from the classic type of biliary colic. Following removal of the gallbladder there is less chance that the patient will complain of pain in the right upper abdominal quadrant. Experimental observations made years ago on patients with regard to the reference of pain following distention of the gallbladder compared with that following distention of the common duct revealed an impressive difference.[1] Distention of the common duct tends to produce high epigastric or substernal pain which often mimics cardiac distress. There is more of a tendency for the patient to complain of nausea and vomiting if the common duct rather than the gallbladder is distended. Shortness of breath also is a more prominent feature of ductal obstruction.

The patient may have an associated pancreatitis, and as a result he may complain of bandlike pain or pain in the left upper abdominal quadrant, depending on the extent of pancreatic involvement. Patients who have had cholecystostomy tend to have pain in the right

upper abdominal quadrant because of the attachment of the fundus of the gallbladder to the overlying peritoneum.

A report of the findings at the time of the primary operation on the biliary tract is essential in the evaluation of persistent or recurrent symptoms. For example it may be found that the gallbladder was not removed. A more conservative approach undoubtedly would be followed if stones had not been found at the initial operation. It also would help to know that a negative cholangiogram was reported at the time of the initial surgical procedure.

Causes of Jaundice

Of the 160 patients who had secondary operations on the biliary tract, 42 per cent had jaundice. If jaundice develops immediately after the first operation and appears to be complete, the dreaded diagnosis of stricture of the common duct must be made. Occasionally an overlooked stone in the common duct may block the duct early in the postoperative period, but this is rather unusual. Transfusion reactions and bile in the peritoneal cavity are other early causes of jaundice. When jaundice develops late, and especially if biliary colic accompanies it, a diagnosis of retained common duct stone is made. Perhaps a cholecystectomy was performed and stones re-formed or were left behind. A retained cystic duct stump may harbor stones which occasionally will pass into the common duct. Recurrent pancreatitis is a more common disease than is generally realized, and may cause compression of the common duct with resultant jaundice. A few cases of cholangitis will defy diagnosis, and in long-standing cases its presence may lead to re-exploration to rule out the possibility of a common duct stone. Recently some authors have recommended prolonged drainage of the common duct in treatment of this condition.

Mistakes have been made in the preoperative diagnosis of the cause of jaundice in 7 to 10 per cent of the cases. Among the reasons for the errors were the following.

1. The jaundice was of such long duration that laboratory data were conflicting. The alkaline phosphatase, elevated early, had returned to normal, and the common tests to demonstrate hepatocellular disease, such as thymol turbidity and cephalin-cholesterol flocculation, were not conclusive.

2. The presence of gallstones was verified and this was assumed to be the sole source of the difficulty. When the presence of a calculus is proved there is a tendency to ignore some of the danger signs insofar as the laboratory tests are concerned. Fortunately this does not happen too frequently in cases of patients who have had previous biliary tract surgery.

3. In a few instances chlorpromazine has been responsible for the simulated obstructive jaundice. The most common difficulty arises from conflicting laboratory data pointing to both surgical and medical types of jaundice.

Since jaundice increases the surgical risk, it is wise to delay the secondary procedure until the cause has been clarified insofar as possible.

Negative Findings at Secondary Operation

Nothing is more discouraging than negative findings at the time of a secondary operation on the biliary tract. In such instances the surgeon must follow through on at least five principles. (1) He must explore the common duct thoroughly, both up toward the liver and down through the ampulla of Vater. (2) An operative cholangiogram must demonstrate absence of disease and a free flow of contrast medium into the duodenum. (3) If there is any doubt as to the patency of the ampulla, it must be visualized by the transduodenal approach. (4) If carcinoma of the head of the pancreas is suspected, the duodenum must be mobilized and a specimen taken for biopsy from the suspicious area if it is superficial and easily exposed. (5) The surgeon should routinely perform liver biopsy in any case in which the patient has jaundice, or if the operative findings are negative. Microscopic examination of the hepatic tissue may be very helpful in certain baffling cases of cholangitis.

Intravenous Cholangiography

This method of visualization of the common duct is well known and is of great useful-

ness provided one adheres to certain standards and technics. Intravenous cholangiography should be considered when a patient has recurrent biliary tract symptoms. If jaundice is subsiding and bilirubin levels do not exceed 3 to 4 mg. per cent, the method may be used with advantage. Obviously a drug should not be injected if there is a possibility of sensitivity on the part of the patient. A test is made by injecting 1 cc. of the contrast material intravenously and then checking the pulse rate and respiration frequently. The potential candidate for anaphylactoid reaction will manifest a definite abnormality in the pulse following this small dose. In actual demonstration of the biliary tree, 15 to 20 cc. of contrast material is injected and films are made. There have been no instances of anaphylactoid shock in this department.

Intravenous cholangiography should not be employed in the presence of increasing jaundice or renal disease. A more unusual complication would be seen in a patient with severe hyperthyroidism undergoing investigation of therapy with isotopes.

In 58 per cent of the cases in which secondary operations on the biliary tract were performed during the past 11 years, intravenous cholangiograms were not made. This figure reflects to some extent the fact that many of these operations were done before intravenous cholangiography became widely accepted and used. In 25 per cent of the cases in which this procedure was employed, the ductal system was not visualized, indicating faulty preparation or selection of patients for this study. When the ductal system was visualized the correct diagnosis was reported preoperatively in 57 per cent, with actual demonstration of calculi in the common bile duct. Even though there was some degree of misinterpretation in the remaining 43 per cent, the intravenous cholangiograms assisted by localizing the pathologic condition and by demonstrating the degree of distention of the common duct.

In preparation for intravenous cholangiography the bowel is cleaned by a saline cathartic given the afternoon before the study. The patient's evening meal is low in fat. Starting at 6:00 P.M. the patient takes 12 contrast tablets at five minute intervals. Water is allowed with the tablets but all other fluids are withheld throughout the night. In the morning the patient is given 10 to 15 mg. of morphine to induce spasm of the sphincter of Oddi, and the preliminary x-ray is taken. If the ductal system is not visualized, 20 cc. of contrast medium is injected and serial films are made to demonstrate appearance of the common duct.

This procedure usually will demonstrate a slightly enlarged common duct in a postcholecystectomy patient. Enlargement beyond 11 mm. is considered abnormal, and beyond 15 mm. definitely pathologic. Recently a large retained calculus was demonstrated in the dilated common duct of a woman who had had cholecystectomy and exploration of the common duct with removal of six calculi more than two years previously. The patient had continued to have symptoms of indigestion without true colic or jaundice. In retrospect in this case it is of interest that a T tube cholangiogram made prior to the patient's discharge from this hospital after the primary procedure clearly demonstrated the calculus in the distal portion of the common duct. Unfortunately the cholangiogram was made after the operative procedure, immediately prior to the patient's discharge, and at that time nothing further was elected to be done. This points up the need for operative cholangiography at the time of surgery.[2] Undoubtedly a second operation would not have been necessary if a T tube cholangiogram had been taken at the completion of the initial procedure.

Investigation to Detect Associated Disease States

As previously mentioned, the clinician should be wary of the possibility of overlooking other diseases when the presence of gallstones has been verified. We recently observed an 85 year old woman who came into the hospital with severe upper abdominal pain and distention. A flat plate of the abdomen disclosed a large solitary calculus in the right upper quadrant in the region of the gallbladder as well as multiple dilated loops of small intestine. It was assumed that the patient had

paralytic ileus as a result of the attack of cholecystitis. Pancreatitis was ruled out by blood and peritoneal fluid amylase determinations. Symptoms subsided promptly under conservative management and the remainder of the gastrointestinal tract was surveyed to determine if the complaints were entirely related to the gallstones. A complete study revealed that the patient not only had gallstones but had a sizable hiatal hernia and a carcinoma of the ascending colon as well as diverticulosis.

The association of hiatal hernia, gallbladder disease and diverticulitis has been documented many times and is generally called Saint's triad[3] (figure 3). This triad should be considered in the investigation of patients having elective biliary operations. We have been repairing an increasing number of hiatal hernias in recent years at the time of cholecystectomy. This has been a planned procedure when the gastrointestinal survey has shown a hiatal hernia of sufficient size to be a possible source of present or future complaints. The surgical approach has been through a high upper midline incision which included the removal of the xiphoid process. This has provided good exposure of the hiatal hernia after mobilization of the left lobe of the liver.

Other diseases such as cardiovascular disease, duodenal ulcer, chronic pancreatitis and carcinoma of the colon must also be considered as possible contributors to the symptoms presented by patients with gallstones (figure 4). Many times it is impossible to tell the difference between coronary disease and common duct colic, since the pain is referred to approximately the same area and is accompanied by shortness of breath.

Technical Aspects of Biliary Tract Surgery

The best way to prevent recurrent symptoms after biliary surgery is to evaluate the patient before the primary operation and then remove all the disease found in the biliary tract.[4] In general it should be anticipated that gallstones will be found at the time of the primary operation in at least 95 per cent of the cases. Regardless of the patient's age, the upper and lower gastrointestinal tract should be

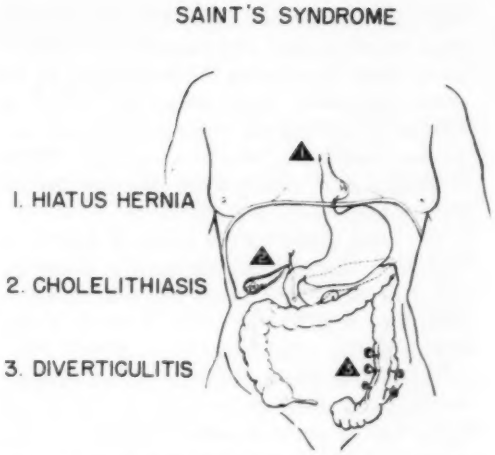
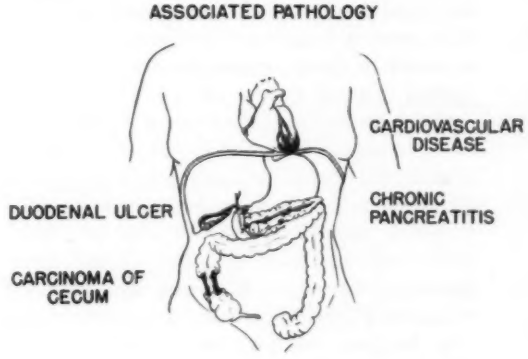


FIGURE 3. The association of hiatal hernia and diverticulitis with gallbladder disease is common.

FIGURE 4. The entire gastrointestinal tract as well as the cardiovascular system must be considered in the differential diagnosis of biliary tract disease.



surveyed by competent roentgenologists. Especially in middle-aged and older groups, the cardiovascular system must be carefully evaluated. Fortunately, cardiovascular disease, which may include a coronary thrombosis six months or more previously, does not contraindicate primary or secondary biliary tract surgery in the presence of proved disease of the biliary tract with recurrent symptoms.

More and more we have been impressed with the safety of removing the gallbladder from the fundus downward after the cystic ar-

tery has been secured. After the liver bed has been approximated, the surgeon can proceed more safely to develop the full length of the cystic duct under direct vision and with little chance of injuring the common duct. It is surprising how many normal variations will be visualized more clearly when this conservative technical approach is utilized.

To avoid injury to the common duct, it is important that the surgeon keep in mind the fact that there are more normal anatomic variations in the region of the cystic duct than anywhere else in the body.

It has been the experience in this hospital that approximately one of every five or six patients having gallstones has a calculus in the common duct. To find these calculi it is necessary to explore the common duct at the time of the primary operation in 40 to 50 per cent of all cases. In recent years the incidence of exploration has decreased to 33 per cent. In some series the percentage is much lower, and consequently there is a drastic reduction in the number of common duct stones recovered. Persistent or recurrent symptoms will occur in many of these patients harboring an overlooked common duct stone.

To make certain calculi are not overlooked in the common duct, an operative cholangiogram at the time of operation seems warranted. Of course this may delay the procedure unless it is well planned in advance with an experienced technical staff to carry out the roentgenologic aspect of this examination. Good equipment, adherence to rules to avoid radiation dangers, and patience are all essential. The anesthetist must be protected from radiation, and all other personnel including the person who has injected the contrast medium should hastily step aside as the roentgenogram is being taken. The polyethylene tube to be passed into the cystic duct stump or the T tube to be placed in the common duct after exploration should first be filled with saline solution to lessen the possibility of air bubbles. Small calculi are more readily discovered if the contrast medium is diluted down to approximately 20 per cent; not more than 5 cc. should be used in the first injection. Ten cubic centimeters or more of solution is necessary in our experience to prove that the contrast medium flows readily into the duodenum and that there is no residual obstruction of the lower end of the common duct.

When the common duct or cystic duct is dilated and the gallstones are small, the common duct has been routinely explored without a preliminary cholangiogram. Two films are taken to provide comparison in questionable cases. In all other instances, even when the common duct is small and the gallstones are large, a small polyethylene tube filled with saline solution is passed into the cystic duct stump and the 20 per cent solution injected. Operative cholangiograms provide the best insurance that the biliary tree is free of calculi and other abnormalities.

It is certainly desirable from every point of view to find and remove all calculi from the common duct at the time of the primary operation rather than to discover an overlooked calculus when a T tube cholangiogram is made 7 to 10 days later. When such an unfortunate situation arises the decision must be made whether to operate immediately or to irrigate the ducts with sterile solutions in the hope the calculi may be washed out. If a large calculus has been overlooked, a secondary operation should be carried out as soon as the patient's condition permits. If the cholangiogram shows small calculi, the possibility of air bubbles or the chance the calculi may eventually pass has been accepted and the T tube is removed. Appropriate equipment for the performance of cholangiography must be provided in any hospital which accepts many patients for biliary surgery.

Reasons for Secondary Biliary Tract Surgery

Of the 160 patients undergoing secondary operations, 48 had had a previous cholecystostomy. In some instances this operation had been done because the patient was a poor risk and the technical difficulties were great. A few elderly patients had a cholecystostomy rather than a cholecystectomy as a treatment of choice.

In 26 other cases the major disease process was believed to be an unnecessarily long or

enlarged cystic duct stump. We have been unable to find a neuroma which might account for the symptoms in any of these 26 cases. In 25 per cent a stone was found in the cystic duct remnant. Patients have been operated on who have had persistent symptoms for as long as 24 years from re-formation of stones in a retained cystic duct stump. Unless the cystic duct remnant contains calculi or is of considerable size, there is reasonable doubt that the symptoms can be ascribed to it.

One of the most common reasons for recurrent or persistent symptoms after biliary tract surgery is a stone in the common duct. One or more stones were removed from the common duct in 50 of the 160 cases, or 31 per cent. The common duct had been explored in 101 cases. This high incidence of recovery of common duct stones gives strong support in favor of operative cholangiography for every patient at the time of primary biliary surgery.

It is distressing to note that in one of every five cases, or 31 patients, operation was performed because of stricture of the common duct. This is always an unfortunate and distressing accident, especially when it occurs in a young patient. The reasons for this catastrophe have been described many times. The surgeon should remember that cholecystectomy may be most dangerous in a very thin patient, since the exposure is so easy and the structures are so relaxed that the common duct may be tented up and mistakenly ligated.

Although the majority of the secondary operations are more difficult than the initial procedures, there were only two deaths in this group of cases.

Conclusion

The indications for secondary operations in cases of biliary tract disease appear all too frequently. Physicians must make a complete survey of the gastrointestinal tract in every patient with gallbladder disease to reduce the need for these operations, and should be aware of the nonsurgical diseases that may be responsible for the patient's symptoms. Perhaps we should make our patients more aware of the secondary diagnosis and warn them that all their symptoms may not disappear after cholecystectomy. The surgeon must be competent to carry out the biliary tract operation with safety. Both physician and surgeon must assume their fair share of responsibility in continuing the improvement of the end results of biliary tract surgery. This increasingly common type of surgery should be accepted in the confidence which it deserves.

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Since the body has no facilities to store oxygen, continuous ventilation of the lungs is required to maintain life. Within the hospital or out, numerous conditions arise which in themselves need not be fatal but which result in death because of associated respiratory difficulties. The author discusses causes of respiratory emergencies and describes simple but effective means of treatment.

Treatment of Respiratory Emergencies

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If breathing stops, life is lost. Since the body has no means of storing oxygen, a constant supply must be assured by continuous breathing. In cases in which an emergency involves both breathing and bleeding, treatment of the breathing difficulty should take precedence. Following cessation of respiration, death occurs within a few minutes, and sometimes in less than one minute. Untreated bleeding, on the other hand, rarely causes death in such a short time.

Difficulties of an emergency nature may arise because of depression of the respiratory center, obstruction of the respiratory passages, or peripheral mechanical changes. Regardless of which mechanism is at work, the end result is hypoxic damage to the vital organs. Among the vital organs first affected by hypoxia is the brain, in which the respiratory center becomes depressed, so that efforts to breathe finally cease.

Respiratory difficulty may arise suddenly in otherwise healthy persons or it may develop gradually as a consequence of chronic illness. Sudden death of respiratory origin may be caused by a head injury, cerebrovascular accident, angioneurotic edema, or convulsive seizure. Slow death due to respiratory failure may follow poliomyelitis, poisoning with depressant drugs, or lesions which encroach on the respiratory passages.

Causes of Respiratory Emergencies

Obstruction of the air passages—In cases of obstruction of the air passages, the tongue drops back in the throat, the epiglottis lies over the larynx, the vocal cords are drawn together, and the patient is unable to get air into his lungs. Foreign bodies may fill the throat. These may include vomitus, blood, secretions, chewing gum, tobacco or dentures. Foreign material may also be aspirated into the lower part of the respiratory tract and occlude the trachea or bronchi.

Among the common causes of this type of

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emergency are conditions which produce unconsciousness, such as cerebrovascular accident, head injury, overdose of sedative or narcotic drugs, and general anesthesia. Whenever a patient becomes unconscious, he loses control of his respiratory passages, and respiratory obstruction is likely to develop.

Obstruction of the air passages may also occur in conscious persons. Children may aspirate into the tracheobronchial tree such objects as nuts, coins, safety pins, and any other materials which they put in their mouths. Patients with muscular dystrophy which impairs the swallowing mechanism, or those with debilitating diseases or poliomyelitis may aspirate food while trying to swallow. If the resulting obstruction is not sufficiently severe to cause sudden death, atelectasis, pneumonitis or lung abscess is likely to follow. The accumulation of secretions in the presence of an impaired cough mechanism has a similar result.

Encroachment on, or narrowing of, the air passages may be caused by changes in the patient's tissues. Inflammatory lesions that may do this include Ludwig's angina, retropharyngeal abscess, diphtheria and other infections which result in tissue edema and thick secretions. Tumors in the air passages, such as polyps or malignant tumors which arise in the pharynx, larynx or bronchi, decrease the lumen of the air passages. Extrinsic tumors, such as enlargement of the thyroid gland or the mediastinal lymph nodes, may narrow the lumen of the air passages by pressure from without.

Decreased or arrested efforts to breathe—Disease or injury of the brain may damage the respiratory center and result in decreasing or absent efforts to breathe. Excessive doses of sedative or narcotic drugs depress the respiratory center, with similar results. Electric shock or lightning, in addition to their other effects, may cause cessation of respiration.

Hypoxia due to any cause depresses the respiratory center of the brain, rather than stimulating it as commonly thought. Respiratory efforts may, in fact, be increased in the presence of hypoxia, but this is temporary and is due to the influence of the carotid body. This control mechanism is activated by hypoxia and functions as an auxiliary respiratory center.

Partial or total inability to breathe may be caused by such diseases as poliomyelitis and Guillain-Barré disease, which involve the neuromuscular system. Excessive doses of anesthetics or muscle-paralyzing drugs similarly interfere with the ability of the patient to ventilate his lungs.

Mechanical problems—The peripheral musculoskeletal system must be intact in order to draw air into the lungs. Multiple fractures of the ribs may produce a flail chest and an inability to create an intrapleural vacuum. Various forms of pneumothorax allow air to enter the pleural space, which causes the lungs to collapse.

The vicious cycle—In many disease conditions, a combination of factors reinforces the harmful effect of each individual factor on the breathing. In cases of diphtheria and laryngotracheobronchitis, there are weakening of the ability to cough, accumulation of thick secretions, swelling of the tissues, and increased oxygen demand due to fever and struggling. In drowning there is aspiration of a small amount of water which causes severe laryngospasm.

In instances of progressive depression of the respiratory center, before complete failure occurs, unconsciousness usually develops and the problem of obstruction of the air passage is superimposed. On the other hand, if mechanical obstruction is the primary difficulty, the development of hypoxia causes depression of the respiratory center so that efforts to breathe finally cease.

Treatment

Removing material from the airway—This can be accomplished by several methods. The simplest one is to insert the fingers into the patient's mouth, and grasp the foreign body or wipe away the secretions. Preliminary wrapping of the fingers with a layer of cloth or gauze is helpful. Gravity can be used in clearing the airway. The patient's head or entire body should be turned to the side, and he should be tilted into the head-down (Trendelenburg) position. If a suction machine is

available, liquid or semisolid material can be aspirated. Large particles block the suction tube and must be removed manually. Foreign material in the trachea or bronchi may be removed by bronchoscopy or by suction through an endotracheal tube.

Establishing a patent airway—This can usually be accomplished by extending the patient's head and supporting his chin. The head may be moved from side to side, and various degrees of extension may be tried to ascertain the most favorable position. If extension of the head and support of the chin do not provide a patent airway, the physician should flex his index fingers and place them behind the angles of the patient's mandible. The lower jaw should then be moved anteriorly as far as possible. This maneuver frequently brings the tongue and epiglottis out of their obstructing position. The physician should stand behind the head of the patient, because in this position he has the greatest mechanical advantage. Another satisfactory method of preventing obstruction by the tongue is to place the fingers under the patient's chin and the thumb on his lower teeth, and then pull the mandible forward. The patient's tongue may also be grasped with a piece of gauze or towel, and pulled forward.

If an oral or nasal airway is available, it may be inserted to help provide a clear air passage. A nasal airway can be quickly improvised by cutting a 6 in. length of rubber tubing, lubricating it, and inserting it through the nostril and into the pharynx. Before this tubing has been advanced its entire length, the patient will be noted to breathe through it.

The insertion of a tube through the larynx and into the trachea may be lifesaving. The technic for inserting this tube probably is the most important thing the physician can learn about resuscitation in cases of respiratory emergency. Intubation of the trachea eliminates obstruction of the upper part of the respiratory tract and permits the use of artificial respiration with the assurance that oxygen and air will enter the patient's lungs. Tracheal intubation also permits aspiration of mucus, blood or vomitus from the tracheobronchial tree if a suction catheter is passed through the endotracheal tube. After aspiration of this material has been accomplished, artificial respiration may be administered effectively with a minimum of effort by any of the common methods.

The insertion of an endotracheal tube is a relatively simple procedure. With instruction by an anesthesiologist or a bronchoscopist, a physician can learn to intubate the trachea in a day or two. Practice on a cadaver enables the physician to master the technic. In an actual emergency, when severe hypoxia is present, relaxation of the patient's muscles occurs and facilitates visualization of the larynx.

If a clear airway cannot be readily established by manipulating the head, mandible or tongue, or by intubating the trachea, a tracheotomy should be performed. This simple procedure is the most valuable of all emergency operations. The physician should not hesitate to proceed with this operation as soon as he sees that other methods are ineffective. It should be done before the patient has become so hypoxic that his vital organs have been irreparably damaged.

If for some reason tracheotomy or intubation of the trachea cannot be accomplished, a lifesaving procedure of temporary value may be utilized. A needle may be inserted into the lumen of the trachea and oxygen administered in a steady stream through the needle. Animal experiments have indicated that large-caliber needles and high flows of oxygen are satisfactory and safe. In human patients, it has been shown that an 18 gauge needle and a flow of 4 l. of oxygen per minute will prevent hypoxia and sustain life. That the point of the needle is within the lumen of the trachea must be demonstrated with certainty before the flow of oxygen is started. This should be determined by repeated aspiration of air with a syringe. Otherwise, subcutaneous emphysema might occur and the patient would receive no benefit from the maneuver. This method of maintaining oxygenation should be used only as a temporary expedient since it does not provide for adequate removal of carbon dioxide. Definitive treatment with endotracheal intubation or tracheotomy should be instituted as quickly as possible.

Artificial respiration—Many methods of artificial respiration have been proposed and have been utilized with apparent success. Since medical evaluation of the patient's condition is not obtained before the emergency treatment is administered, one cannot be certain of the actual benefit derived. Artificial respiration may not only be unnecessary, it may be actively resisted by the patient, but it may be credited for the patient's recovery. No method of artificial respiration can be satisfactory unless a clear airway is assured, nor can the method be successful unless it is carried out properly. Most physicians are not sufficiently familiar with the standard technics to use them efficiently.

The physician can, however, do a more effective job than trained first-aid workers by utilizing mouth-to-mouth breathing. This has the advantage that the physician can extend the patient's head, support his chin, maintain a clear airway, and at the same time inflate the patient's chest with his exhaled breath. He is able to utilize positive pressure of air from his own exhalations, and he should see the patient's chest expand with each breath. This is far more satisfactory than the standard methods, and provides, in addition, visual evidence that the artificial respiration is effective.

Modifications of the mouth-to-mouth breathing technic include blowing into the endotracheal tube or into the oral airway if either is used. A convenient method is to utilize two airways joined together. One is inserted into the patient's mouth, and the physician blows into the other.

If a mechanical device that utilizes oxygen for artificial respiration is available and in working order, its use is, of course, recommended. One must not wait for the arrival of such a device, however, and the real saving of life is most often accomplished before the machine becomes available. Complicated devices for the administration of artificial respiration are not necessary. Each physician can readily make available for himself a simple device which is not likely to be out of order when needed. This simple device consists of a breathing bag, a mask, and a tank of oxygen. These items can be purchased separately from surgical supply houses, and can be assembled by the physician. Simple, practical and inexpensive devices may be purchased already assembled.

Treatment of respiratory emergencies in infants and children—In respiratory emergencies in infants and children, the need to breathe and the problems which arise are similar to those in respiratory emergencies in older patients. The danger is greatest at the time of birth, during severe illness, and in the immediate postoperative period. In small patients, the difficulties are magnified because of the smaller lumina of the respiratory passages. Slight swelling and small accumulations of secretion decrease the lumen of the air passage by a much greater proportion than in adults. The problem is further aggravated because an infant or child has a weaker musculature, a less active respiratory center in the brain, and a softer thoracic cage. As a result, he does not try so hard to breathe and his chest tends to retract more readily than that of an adult. For this reason, filling of the lungs with air is not accomplished.

Since the respiratory problems of small patients tend to be more serious and to develop more abruptly than those of older persons, treatment must be instituted with the utmost promptness. The nature of the treatment is similar to that which has been described for adults.

Conclusions

In any emergency situation, the restoration of breathing takes precedence over all other problems. In dealing with a respiratory emergency, the principles of treatment include removal of foreign bodies, establishment of an unobstructed airway, and effective artificial respiration.

The most satisfactory method of artificial respiration is one which permits positive pressure inflation of the patient's lungs. This can be accomplished with mouth-to-mouth breathing, or with a device which utilizes oxygen under positive pressure. Visible inflation of the patient's chest provides proof that the artificial respiration is effective.

To maintain life, maintain the breathing.

Increasing understanding of the group A streptococcal etiology of rheumatic fever has resulted in great advances in controlling the disease. Of the many antibiotics effective against group A streptococci, the sulfonamides, orally administered penicillin, and repository benzathine penicillin have been used most extensively to control rheumatic recurrences. Studies at the Warren Air Force Base have indicated that initial attacks of rheumatic fever may be prevented by prompt and adequate penicillin therapy of the antecedent infection.

The Etiology and Prevention of Rheumatic Fever

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DURING the past 50 years, a great wealth of indirect but overwhelming evidence has accumulated which incriminates the group A *Streptococcus* as the major, if not the sole, etiologic agent of rheumatic fever. Despite the increasing clarity of this concept, the riddle of the exact pathogenesis of the disease continues to perplex and intrigue the student of infection and allergy.

Pathogenesis

Although intensive efforts have been made to induce rheumatic fever by various means in experimental animals, as yet they have not been successful. These investigations have usually been marked by the consistent failure to reproduce a disease which critical gross and microscopic criteria determine as identical with rheumatic fever.

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After many months of intensive experiments, Murphy and Swift[1,2] induced myocardial and vascular lesions similar to those characteristic of human rheumatic heart disease in only a few of many rabbits repeatedly infected focally with group A streptococci of several virulent serologic types. These lesions were not found in appropriate controls of untreated rabbits. If the lesions were actually due to rheumatic fever (and they certainly appeared to resemble human Aschoff's bodies more closely than those produced by any other experimental model), this investigation adds evidence to the generally accepted clinical concept that repeated infections with group A streptococci result in rheumatic fever. The tedious and laborious nature of the experiments, however, is discouraging to the prospect that this line of approach will readily elucidate mechanisms of the pathogenesis of the disease in animals. Indeed, it suggests that to create the special conditions necessary to initiate the rheumatic process requires a long and complicated series of events comparable to the natural history of the disease.

Since the early classic studies of Von Pirquet and Schick[3] on serum sickness and of

Escherich and Schick[4] on scarlet fever, it has been a general assumption that rheumatic fever represents some form of hypersensitivity to infection. It must be admitted, however, that 50 years after the stating of this hypothesis we are not able to present any definitive evidence to substantiate the concepts of those astute senior clinicians. The mechanisms of various kinds of necrotizing allergic reactions have been used extensively as a pattern for attempts at the experimental production of rheumaticlike lesions. All these approaches have been limited by the lack of specificity of the experimentally induced lesions. In the absence of a pathognomonic test or reaction for rheumatic fever, investigators have had to depend solely on morphologic criteria which have not been entirely convincing and cannot be identified unequivocally with the lesions of rheumatic fever.

Clinicians have sought in vain for either a general allergic diathesis in the rheumatic fever patient or an atypical immune response to streptococcal infection. Rheumatic patients have not given a personal or family history of increased incidence of common allergies such as hay fever, bronchial asthma, urticaria, eczema or drug hypersensitivity. There is, as yet, no clinical test for the detection of an allergic reaction in rheumatic patients which does not occur in other patients recovering from a streptococcal infection or from certain other diseases.[5]

If the foregoing brief review paints a somewhat discouraging picture of our understanding of the pathogenesis of rheumatic fever, the ensuing discussion should be much more heartening. It will be concerned with the practical potentialities for controlling the disease which have evolved from an increasing understanding of the relationship of the group A *Streptococcus* to the natural history of rheumatic fever and from the great advances made in controlling infection by antibiotic therapy.

Relationship of Group A Streptococcus to the Natural History of Rheumatic Fever

The etiologic relationship of the group A *Streptococcus* to the natural history of rheumatic fever is determined by four major types of evidence: clinical, immunologic, epidemiologic and prophylactic.

Clinical evidence—For at least two centuries physicians have noted an association between sore throat and acute articular rheumatism. However, not until the latter part of the nineteenth century did well-documented case studies appear which emphasized the high incidence of tonsillitis and pharyngitis preceding the acute rheumatic attacks. With the rise of the science of bacteriology and after attention had been focused on the *Str. pyogenes* as the cause of scarlet fever, this organism was more frequently implicated as the agent associated with the prerheumatic respiratory infection. Lancefield's antigenic classification of the *Streptococcus* narrowed the focus further on group A organisms. The subsequent impressive epidemiologic and bacteriologic studies of Coburn[6] in 1931 laid the foundation for the modern etiologic concept of the causal role of group A streptococcal infection in rheumatic fever. In the same year, Collis[7] independently demonstrated the same sequential causal relationship.

Despite these impressive studies many clinicians were still reluctant to regard this association as invariably significant. Still to be explained was the common observation that some rheumatic attacks appeared without apparent preceding streptococcal infection. This puzzling observation has subsequently been explained by the intensive study of the immunology of the *Streptococcus*. This has revealed the large number of streptococcal infections which occur without apparent clinical symptoms and has shown the frequency with which clinically inapparent streptococcal infections can result in rheumatic fever.

Immunologic evidence—In 1932, the studies by Todd[8] of the method for titrating antistreptolysin in serum began an era of streptococcal immunology that brought forth a wealth of serologic evidence documenting the frequency of antecedent streptococcal infection in initial and recurrent rheumatic attacks. Numerous antigenic extracellular products of the *Streptococcus*, such as hyaluronidase, streptokinase (fibrinolysin), desoxyribonuclease and

diphosphopyridine nucleotide, to name but a few, subsequently were found to have specific human serum antibodies directed against them. Detection of a battery of these antibodies in human serum now makes the diagnosis of recent streptococcal infection highly sensitive and accurate. McCarty[9] and Stetson[10] have reviewed some of the evidence that relates the immune response in rheumatic fever to precursory streptococcal infection. Long-term immunologic studies of rheumatic subjects now indicate that virtually all initial and recurrent attacks of rheumatic fever can be shown to be associated with recent streptococcal infection.[11]

Study of the immune response in rheumatic subjects has not revealed, however, any bizarre, atypical or characteristic response that cannot be found in any nonrheumatic persons who have been exposed to intense streptococcal infection. Almost all studies have shown that antibody titers against streptococcal antigens are greater in rheumatic subjects than in control populations. This has suggested to some that the rheumatic person has an abnormally reactive immune response. When rheumatic subjects have been tested carefully, however, by using quantitative immunochemical methods after the injection of various purified nonstreptococcal antigens, there has been no qualitative or quantitative difference in their antibody formation (including skin-sensitizing antibodies) compared with the antibody response of nonrheumatic subjects.[9] It would be more consistent with classic immunologic thinking to regard the high level of streptococcal antibodies found in the acute stage of rheumatic fever simply as evidence of repeated or intensive streptococcal infection.

The long list of extracellular and somatic products which have been isolated from the group A *Streptococcus* has failed so far to reveal any substance or antibody to any substance which can be related specifically to the pathogenesis of rheumatic fever. However, laboratory tests for various streptococcal antibodies in the study and management of rheumatic fever have a great deal of practical clinical usefulness.

Epidemiologic evidence—Prior to World War II many studies emphasized the close parallel in the clinical, geographical and seasonal epidemiology of rheumatic fever and streptococcal infections. But the opportunities afforded well-trained investigators equipped with the means for careful bacteriologic and immunologic study resulted in a brilliant documentation of streptococcal epidemics and rheumatic fever by the armed forces. Rammelkamp, Denny and Wannamaker[12] have presented extensive data to indicate that the environmental, bacterial and host factors which appear to play a role in the development of rheumatic fever are important primarily as they are related to the incidence of preceding streptococcal infection.

Thus, such factors as latitude, altitude, crowding, dampness, economic situations and age all affect the incidence of rheumatic fever, as they are related to the incidence of streptococcal infections in general. No particular strain of group A *Streptococcus* or serologic type has been associated with rheumatogenicity. As a matter of fact, the attack rate of rheumatic fever following proved streptococcal infection at Warren Air Force Base was found to be remarkably constant (about 2 to 3 per cent), regardless of the streptococcal strain, the season or the year in which the study was made. It was pointed out that this attack rate was similar to that observed in other reported streptococcal epidemics in different years and different parts of the world.

The most clearly defined of the many factors which modify this attack rate appears to be the intensity of the immune response as measured by the rise of antistreptolysin O titer. In general, the highest attack rates have been found in groups of patients who have the highest convalescent antibody titers. The age incidence of rheumatic fever indirectly confirms this concept. The condition is rare in infants with a feeble antibody response following their first or second streptococcal infection, whereas the peak incidence falls in the school-age population between the ages of 6 and 10 years when the highest levels of streptococcal antibody titers are found and when streptococcal infection is most intense.[13] Thereafter, the observed incidence of acute rheu-

matic fever declines with age, unless an older population is exposed to epidemic conditions, which may cause the attack rate to become very high.

In this regard it is of interest to note the relative infrequency of overt rheumatic fever in certain semitropical climates where streptococcal infection has been studied in school children. In Miami, Florida, very few cases of rheumatic fever are reported despite the rather high frequency with which group A streptococci can be isolated from throat cultures made routinely in school children throughout the year.[14] It is highly significant, however, that the antistreptolysin O titers observed in these children are very much lower than those seen in the same age group in large cities of the temperate zones of the United States and that the magnitude of the rises reported is small compared with that in children infected with streptococci who live in areas where rheumatic fever is relatively common.

Furthermore, there is little doubt that a previous attack of rheumatic fever markedly increases the risk of recurrent attacks following a streptococcal infection. Recurrence rates of 50 per cent or more have been observed in outbreaks of streptococcal epidemics among children convalescing from recent rheumatic attacks[12] and among rheumatic children who have not been kept on continuous prophylaxis against intercurrent streptococcal infection.[15]

This high susceptibility to reactivation of rheumatic fever following streptococcal infection in the rheumatic patient raises several important questions: Is the rheumatic subject genetically predisposed to react in this fashion to a streptococcal infection, and will he do so throughout life whenever he encounters the *Streptococcus*? Or, is the rheumatic state an acquired form of hyperreactivity in certain predisposed hosts which has developed as a consequence of intensive streptococcal infection? If the latter is true, will such hyperreactivity wear off in time if there is prolonged protection from any subsequent streptococcal infection?

Following an attack of rheumatic fever, the incidence of recurrence is greatest in the first few years of convalescence. Thereafter, the recurrence rate declines sharply. Whether this sharp decline is due to less frequent streptococcal infection in older individuals, to less hyperreactivity to streptococcal infection with the passage of time, or to other host factors which change with the aging process is not yet known; but these theories are being studied carefully in some centers where long-term prophylactic programs are in operation.

Prophylactic evidence—Perhaps the most dramatic line of evidence for the relationship of the group A *Streptococcus* to rheumatic fever has been the increasing realization that the proper treatment and control of streptococcal infection will reduce the incidence, morbidity and mortality of rheumatic attacks. This evidence has been presented in detail in several recent reviews.[16-18]

There are now at least two effective approaches to the prevention of rheumatic fever through the use of antibiotics: (1) protection of the highly susceptible rheumatic patient from repeated attacks of the disease by maintaining continuous chemoprophylaxis against new streptococcal infections and (2) prompt and adequate treatment of streptococcal pharyngitis in the general population to reduce the incidence of initial attacks of rheumatic fever.

Prevention of Rheumatic Recurrences

Many antibiotics are effective against group A streptococci. The following discussion is confined to an evaluation of three methods that have been employed most extensively for the prevention of rheumatic recurrences.

Sulfonamides—Many controlled independent studies during the past 20 years and a vast military experience during World War II[19] demonstrated conclusively that daily oral administration of small doses of sulfonamides will reduce the incidence of rheumatic recurrence by at least 85 per cent. Among the sulfonamides, sulfadiazine is generally considered the drug of choice, although some of the newer, more soluble sulfonamides may be equally effective. Sulfadiazine is inexpensive, easily administered and well absorbed from the gastrointestinal tract; its effectiveness is established.

There are several disadvantages to this

method. Frequent breaks in the routine occur, because patients are apt to forget to take medication daily. There is no practical way to determine whether the occurrence of a streptococcal breakthrough is due to failure of the drug to protect or to a lapse in the regimen. Another disadvantage is that the action of sulfonamides is bacteriostatic rather than bactericidal. The sulfonamides do not eradicate the *Streptococcus* from the throat of the infected patient or the convalescent carrier. In addition, sulfonamide-resistant streptococci have appeared during mass prophylaxis programs. However, such strains do not now constitute a serious threat because of the availability of other effective antibiotics. Finally, the risk of occasional serious toxicity, particularly granulocytopenia, is sufficient to require routine white blood cell counts during the first few weeks of the prophylactic regimen.

The daily dose of sulfadiazine recommended is 1.0 gm. Some advise this as a single daily dose; others prefer that 0.5 gm. be given twice daily. Toxic reactions to such small doses are infrequent. Mild reactions such as skin rashes occur in about 0.5 per cent of cases. More serious reactions, such as agranulocytosis and exfoliative dermatitis, occur in about 1 in 10,000 patients.[19]

Orally administered penicillin—Until recently there were relatively few extensive controlled studies in which penicillin was administered orally in small daily doses to prevent rheumatic recurrences. Theoretically and from scattered early reports, this method should be at least as effective as the use of sulfonamides. Studies in the armed forces[20] indicated that daily doses of as little as 100,000 units of orally administered penicillin were highly effective in protecting troops from infection during epidemics of streptococcal pharyngitis. Such small doses do not seem quite adequate to protect the highly susceptible rheumatic patient from recurrences of rheumatic fever.

In the most extensive controlled study reported on this point,[21] it was found that 200,000 units of penicillin administered daily as a single dose to a large group of rheumatic patients did not afford greater protection than a single daily dose of 1.0 gm. sulfadiazine; indeed, it may actually have been inferior. To improve on the results obtained with orally administered sulfonamides, it may be necessary to employ a tablet of 200,000 units of penicillin twice daily, a regimen which is limited by its considerably greater cost.

Penicillin has several innate advantages, however, over sulfonamides. It is a more effective antibiotic against group A streptococci, and its action is bactericidal rather than bacteriostatic. In adequate doses it will eradicate the *Streptococcus*. Serious toxic reactions are quite rare with the small doses given orally for continuous prophylaxis. Penicillin-resistant group A streptococci never have been encountered despite the extensive use of this compound. Increased resistance of other flora of the throat with these small doses has not been a problem.

Most of the penicillin reactions encountered with the use of prophylactic doses of penicillin given orally have been mild and transient and usually have consisted of generalized urticaria. In most instances if penicillin is discontinued for a few days it can be restarted orally without causing further reactions. When reactions are more severe and associated with angioneurotic edema, penicillin should be discontinued and sulfonamides substituted. Even these reactions, however, do not necessarily indicate permanent sensitization to penicillin.

Repository benzathine penicillin—The major disadvantage of daily, orally administered prophylactic medication is that ambulatory patients are apt to forget to take tablets regularly. The development of the slowly absorbed repository penicillin salt, benzathine penicillin, has been a major practical advance in penicillin therapy. The injection of 600,000 units of this compound provides low serum levels of penicillin for 12 to 14 days. A single injection of 1.2 million units results in detectable penicillin levels in the blood for as long as three to four weeks.[17]

Monthly intramuscular injections of 1.2 million units of benzathine penicillin have proved very effective in preventing streptococcal infections and recurrences of rheumatic fever. Indeed, carefully controlled studies in matched groups of patients have shown this

method to be the most effective yet employed for continuous prophylaxis. In two recent studies it was shown that when patients on this regimen were followed for a total of 432 patient-years, there was not a single recurrence of rheumatic fever in a school-age group of patients who had had rheumatic fever within two years of the onset of the prophylactic regimen and who were exposed to social and economic conditions known to result in the highest incidence of new rheumatic attacks.[21, 22] Several other studies have confirmed the effectiveness of this regimen.

The major disadvantage of administering penicillin by injection is the inconvenience and pain caused the patient. The site of injection tends to be somewhat more painful with the use of this compound than with procaine penicillin, particularly in the very young age group. Severe local reactions resulting in abscess formation have not been observed. Occasionally, however, local soreness may be attended by mild fever lasting two or three days. These reactions are due to the local irritation of the medication in the tissues and subside promptly when the local reaction subsides.

Actual hypersensitivity reactions have not been more frequent or more severe with the use of this compound than with the parenteral use of other forms of penicillin. Reactions have been somewhat less frequent in children than in adults; however, even in the latter, recent extensive studies of repeated injections during mass prophylaxis studies in the armed forces have not revealed any serious problem of hypersensitivity reactions from even prolonged and intermittent administration of this compound.[23]

There are two major questions for which there are as yet no definite answers: What is the risk of streptococcal infection to the adult who has had rheumatic fever in childhood but who has had a long asymptomatic interval since then? Should the adult with rheumatic heart disease and no recent history of rheumatic fever (or no history of rheumatic fever at all) be required to remain on prophylaxis indefinitely?

As previously discussed, the answers to these questions require data that are not yet available. Little is known about the actual frequency of clinical and subclinical streptococcal infection in adult rheumatic cardiac patients. More important, little is known about the danger of such infections in reactivating rheumatic fever in this group compared with the rheumatic patients who have recently recovered from rheumatic fever. It is known that in the latter group there is a great risk that rheumatic fever will be reactivated by even a mild or clinically inapparent streptococcal infection (that demonstrated by rise in antibodies and positive throat cultures in asymptomatic persons). In 96 streptococcal infections which occurred as a breakthrough of prophylaxis in one study, there were 13 consequent recurrences of rheumatic fever. This is striking when one considers that most of these breakthroughs were asymptomatic and detectable only by immunologic and bacteriologic studies.[21]

If the rheumatic subject no longer reacts the same way to streptococcal infection after a prolonged period of prophylaxis, there will be a better basis for a decision regarding the duration for which it must be maintained. Such studies should yield some important fundamental theoretical information concerning the nature of the rheumatic host. Is the patient's rheumatic reaction to streptococcal infection a constant genetic predisposition or one that is acquired and that decreases with the duration of freedom from infection?

Prevention of Initial Attacks of Rheumatic Fever

The most recent chapter in the long story of the relationship of the group A *Streptococcus* to rheumatic fever has been the demonstration that *initial* attacks of rheumatic fever in the general population may be prevented by prompt and adequate penicillin therapy of the antecedent infection. Certain chemotherapeutic principles on which this preventive approach is based have been firmly established as a result of the admirably controlled large-scale studies conducted at the Streptococcus Disease Laboratory at Warren Air Force Base.[24] These principles may be summarized in the following manner.

To prevent the complication of subsequent rheumatic fever, group A streptococci must be eradicated completely from the nose and throat of the patient who has streptococcal pharyngitis. Clinical cure of the signs and symptoms of the infection is inadequate if organisms persist after treatment. Sulfonamides, which are bacteriostatic, do not eradicate the *Streptococcus*. Penicillin, although a powerful bactericidal agent, must be administered well beyond the clinical cure to eradicate permanently streptococci from the throat.

The therapeutic regimen required to achieve this bacteriologic cure has been clearly defined. If penicillin is administered orally, a minimal daily dose of 500,000 units must be given for at least 10 days. Larger doses given for shorter periods are less effective. If penicillin is administered parenterally, any schedule may be employed which maintains effective blood concentrations of penicillin for a 10 day period. Group A streptococci are invariably sensitive to penicillin levels of less than 0.04 unit per milliliter in vitro. Therefore, the blood concentration need not be high to achieve a maximal killing effect in vivo. Once these low blood levels have been achieved, the efficiency of chemotherapy is a function of the duration for which they are maintained.[25]

Various blood levels of penicillin result from the administration of different forms of injectable penicillin. Very high levels result from the injection of 600,000 units of penicillin G, but these last only a few hours. The same dose of aqueous procaine penicillin produces lower levels lasting for two days. When procaine penicillin is combined in oil with aluminum monostearate, the levels are still lower and last four to five days. The same dose given as an injection of benzathine penicillin will provide still lower levels, but these last from 10 to 14 days and are quite adequate to cure most cases of streptococcal pharyngitis.[17] Therefore a single injection of benzathine penicillin, particularly in a larger dose of 1.2 million units, will achieve a cure of streptococcal pharyngitis, both clinically and bacteriologically, with as great efficiency as any other course of penicillin administered in any dose for 10 days.[26]

A single large dose of procaine penicillin will produce only a temporary disappearance of streptococci from the throat. Within a few days most patients will have a bacteriologic relapse. On the other hand, if 600,000 units of procaine penicillin is given every other day for four doses, the bacteriologic cure rate will be about 95 per cent. The same cure rate will result from a single injection of 1.2 million units of benzathine penicillin.

The treatment of streptococcal infection with tetracycline compounds or with erythromycin for 10 days also eradicates the organism from the throat and reduces the incidence of rheumatic sequelae.[27] These broad-spectrum antibiotics may be reserved for those patients who are hypersensitive to penicillin.

It is apparent that the major limitations of the chemotherapeutic approach to the prevention of initial attacks of rheumatic fever are the difficulty of clinically identifying streptococcal sore throat and the fact that at least one-third of patients with acute rheumatic fever do not appear to have had a clinically apparent infection that would have been brought to the attention of the clinician for treatment. It is important to avoid the promiscuous and unnecessary administration of penicillin to patients with viral upper respiratory infections. Simple coryza, hoarseness and tracheitis are rarely due to streptococci. The syndrome of sudden onset of fever, sore throat, "beefy" redness, and pharyngeal exudate suggests the diagnosis with about 70 per cent accuracy.[28] In infants and very young children, however, the difficulties of diagnosis are far greater, because these symptoms and signs are less apparent. Furthermore, very mild-appearing signs may be due to streptococcal infection, and, conversely, some viral infections produce exudates and signs identical with those of streptococcal pharyngitis.

For this reason, the throat culture is an invaluable guide to the indications for therapy. Withholding therapy for 24 hours and waiting until a preliminary report is made of the presence or absence of hemolytic colonies on a sheep's blood agar plate inoculated with a throat swab[29] will not jeopardize the patient's recovery or the prevention of rheumatic fever.

Indeed, it is only by the use of throat cultures that the treatment of upper respiratory infections can be placed on a sound scientific basis at the present time. It is well to remember that more than 90 per cent of upper respiratory infections are due to viral rather than to bacterial causes.

It is obvious that the chemotherapeutic approach to the prevention of initial attacks of rheumatic fever is not the final answer. But the proper diagnosis and treatment of streptococcal infection will certainly greatly reduce its prevalence. The effect of mass prophylaxis with single injections of benzathine penicillin or with courses of orally administered penicillin has already greatly reduced the frequency of epidemics of streptococcal infections in the armed forces and in civilian populations, with consequent striking reduction in the incidence of subsequent rheumatic fever. Widespread intensive streptococcal infection may be sharply curbed in the civilian population, and this may have a profound effect on the attack rate of rheumatic fever.

There is considerable question as to whether or not the 3 per cent attack rate of rheumatic fever observed following the kind of streptococcal infection encountered in epidemics and in military populations applies to the sporadic type of streptococcal infection seen in civilian medical practice. The latter infection is often due to less virulent strains, and for this and other reasons the attack rate of rheumatic fever may be much lower if the frequency and intensity of streptococcal infection are controlled by adequate therapy. Studies of the factors influencing the attack rate of rheumatic fever following streptococcal infection in the civilian population are, in fact, sorely necessary for theoretical reasons as well as for the practical reason of determining the exact indications for intensive penicillin therapy in this group.

Comment

Despite the elusive nature of the pathogenic mechanism of rheumatic fever, the painstaking and piecemeal collection of a vast number of facts has led to the modern concept of the group A streptococcal etiology of rheumatic fever and to methods which have opened a new era for the control of this and other streptococcal diseases.

Approaches to many of the unknown questions of rheumatic fever and rheumatic heart disease have been made possible by these advances. The application of highly efficient prophylactic measures combined with careful immunologic and bacteriologic studies should determine in the near future to what extent control of streptococcal infection in the rheumatic patient will influence the rheumatic state and the natural history of rheumatic heart disease. Pending more basic knowledge of the nature of the disease process, the practitioner faces rheumatic fever today with at least some knowledge of the adversary and with some effective, if crude, offensive weapons.

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A Special Issue

Cardiovascular Diseases

In May

The cause of primary biliary cirrhosis is unknown. It quite probably is a symptom complex rather than a disease entity. It begins insidiously, occurring almost exclusively in women. Pathologic findings are variable. Evaluation of treatment is difficult and prognosis is ominous. Nine cases with varying clinical and biochemical findings are presented. Steroid therapy in five cases proved generally disappointing. The author suggests further study of linoleic acid therapy, used to diminish total lipid formation.

Primary Biliary Cirrhosis

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SINCE the original description of hypertrophic biliary cirrhosis offered by Hanot,[1] a symptom complex with many of the features of biliary obstruction but associated with patent extrahepatic bile passages has been reported under a variety of diagnostic or descriptive terms, such as biliary cirrhosis, cholangiolitic cirrhosis, and cholostatic jaundice. It is of some historical interest that Addison and Gull[2] described hepatic cirrhosis with xanthomatous lesions more than 20 years before Hanot's publication.

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It has long been recognized that the clinical signs and biochemical abnormalities of what is now called primary biliary cirrhosis approximate very closely those of some cases of prolonged extrahepatic biliary obstruction.[3] The association of both intrahepatic and extrahepatic forms of the condition with xanthomatosis is clearly established; formerly some workers regarded the xanthomatous form of the disorder as a separate entity.[4] Recently a form of chronic hepatic disease with obstructive jaundice identical with the primary nonobstructive variety of biliary cirrhosis has been described following the administration of certain drugs (methyltestosterone, arsenicals, chlorpromazine). The similarity extends even to the formation of extensive xanthomas.[5] The obstructive form of biliary cirrhosis may be reversible even at a late date if the extrahepatic block is removed. The chemotoxic form likewise may be curable after the offending drug is discontinued, but the primary idiopathic form of the disorder appears to be irreversible and progressive.

Primary biliary cirrhosis is not a particularly common condition. Ahrens and associates,[6] reviewing the literature prior to 1950, collected 25 cases of confirmed primary cirrhosis with xanthomatosis plus 17 in which extrahepatic obstruction was not completely excluded, and added 17 cases of their own. Hoffbauer[7] reported on 30 cases collected at the

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University of Minnesota between 1945 and 1956. Ricketts and Wissler[8] recently described nine carefully studied cases.

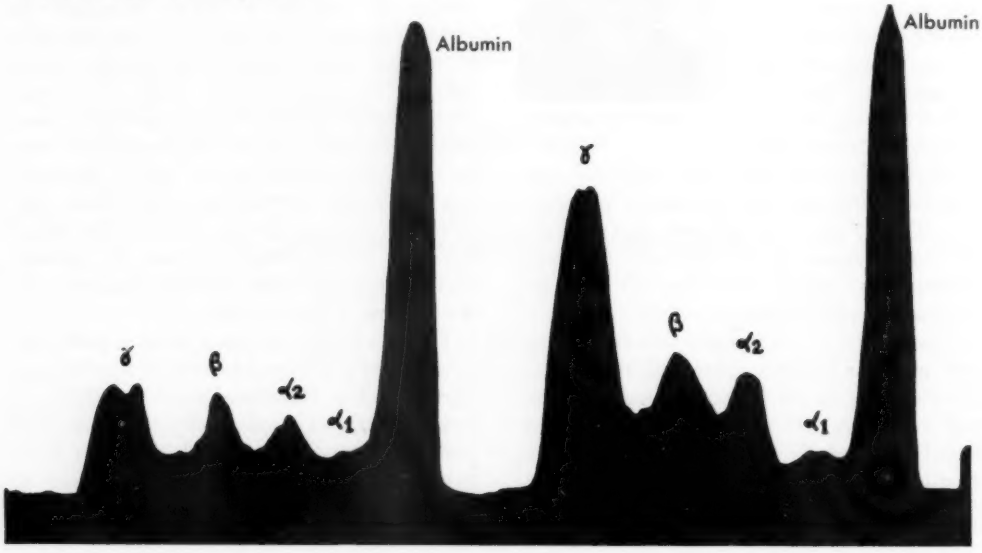
Detailed description of the syndrome can be found in the reviews of Kunkel[9] and of Ahrens and associates.[6] Affecting women almost exclusively, it usually begins insidiously with malaise, fatigue and pruritus, the latter being the most troublesome and persistent symptom. Slight painless jaundice and melanosis may appear early. Often there is progressive lichenification of the skin associated with recurrent papular or factitious dermatitis. Most patients are well nourished, and many have little disability aside from that caused by severe itching. The liver may be moderately or greatly enlarged. Splenomegaly is usually noted. Clubbed fingers are seen occasionally.

Associated biochemical disturbances include hypercholesteremia, increased phospholipid and total lipid content of the serum, and greatly elevated lipoproteins. The serum does not become opalescent, presumably because of the high phospholipid content. Alkaline phosphatase is greatly elevated. Hyperbilirubinemia is a variable feature; normal biliary flow into the duodenum is the rule. Beta and gamma globulins usually are increased (figure 1) although the serum albumin remains normal until late in the course of the disease. Other tests of liver function, except BROMSULPHALEIN® excretion and radioiodinated rose bengal, do not show much disturbance. Because of the high lipoprotein fractions, positive thymol turbidity tests are frequently observed, notably in cases of long duration.

A remarkable feature is the development of xanthomatosis at a critical level of blood lipids. As Ahrens and co-workers[6] demonstrated, xanthomatous lesions appear when the level of blood lipids is in the neighborhood of 1800 mg. per 100 cc. Above this point, xanthelasma, xanthoma planum and xanthoma tuberosum appear, in about that order. These may be extensive and disfiguring. As the hepatic parenchyma deteriorates later in the disease, serum lipids may fall and xanthomas disappear. Other metabolic features of the disease include a marked defect in intestinal absorption of fat, generalized osteoporosis,[10] at times associated with pathologic fractures, and elevated basal metabolism without the presence of hyperthyroidism.

Since this type of biliary cirrhosis has been

FIGURE 1. Electrophoretic pattern in case 3 (right) compared with a normal adult pattern (left). Elevation of beta and gamma globulins is conspicuous.



described almost exclusively in women, the endocrine aspects have quite naturally been studied. Administration of estrogenic compounds produces a rise in phospholipids, neutral fats and total lipids, with a small rise in cholesterol. Under such circumstances the serum may become opalescent, but withdrawal of the drug causes prompt clearing and a return of the blood fats to previous levels. A fall in all lipid components may follow administration of methyltestosterone, with relief of itching, but a marked rise in bilirubin also may occur. These changes also are reversible by discontinuing the drug.

While the course of the disease is inexorably downward, relapses and remissions of variable degree are common and thus evaluation of treatment is difficult. In some instances the disease appears to remain stationary for long periods. The later stages are characterized by the signs of portal hypertension with formation of esophageal varices, and still later by the signs of hepatic insufficiency. In Hoffbauer's series, 11 of the 14 patients whose disease terminated fatally had ascites at the time of death.

Etiology

As indicated earlier, the cause of the disease is unknown. The sex linkage, the lack of any history of exposure to hepatotoxic agents, and the good nutritional status of most patients are among the puzzling features. It is likely that more than one etiologic agent eventually may be recognized. Quite probably we are concerned with a symptom complex and not a disease entity. The condition often is listed among the disorders of fat metabolism, a classification that must be disputed because it can be duplicated so closely in certain persons by prolonged obstruction of extrahepatic bile passages. The possibility of an autoimmune reaction is by no means excluded. Mackay[11] recently reported a case with marked complement-fixing antibodies for human tissue antigens.

Watson and Hoffbauer[12] considered the relation of primary biliary cirrhosis to a previous "cholangiolitic" type of hepatitis. They studied a group of eight patients (five men and three women) who presented the syndrome of chronic jaundice, hepatomegaly, pruritus, and retention in the blood of three substances ordinarily excreted in the bile, namely, cholesterol, bilirubin and alkaline phosphatase. Blood cholesterol and phosphatase were not markedly abnormal in any of the cases. Serum bilirubin ranged from 4 to 30 mg. per 100 cc. In all the cases the essential metabolic functions of the liver were normally preserved. Some of the patients improved and eventually reached a fairly normal state of health. In contrast, one patient (their case 8), followed more than 30 years, had progressive deterioration of liver functional status and died as a result of hemorrhage. These authors raised the question whether some chemical or viral stimulus may persist and cause proliferation of connective tissue and slow strangulation of the liver lobule. They considered the virus of infectious hepatitis the likeliest suspect. Their cases and certain others of the same type which have been reported emphasize the need for immunologic or serologic methods to identify a previous infection with hepatitis virus.

Pathology

As might be expected, pathologic findings in the liver are variable in the extreme, ranging from lymphocytic infiltration with bile staining to a condition virtually indistinguishable from various other types of cirrhosis. The earliest lesions are nonspecific inflammatory reactions in portal and periportal areas with associated bile duct proliferation and signs of bile stasis. The inflammatory reaction involves the perilobular and intralobular ductules and, as Popper and Elias[13] have shown by three-dimensional technics, forms a cylindric network that traverses the lobules. The lobular pattern is not greatly distorted and nodular regeneration is not marked until late in the disease.

It is apparent from the foregoing that the diagnosis of primary biliary cirrhosis by means of biopsy of the liver is not simple. Even the most experienced pathologist will admit, as Hoffbauer[7] does, that classification of many types of cirrhosis solely on the basis of histologic appearance is virtually impossible.

This applies with particular force to the diagnosis of biliary cirrhosis; without other biochemical data and sometimes without positive evidence of patent extrahepatic bile passages a positive commitment cannot be safely made.

Clinical Course and Effects of Treatment

This report is concerned with nine cases seen in private practice during the past six years. Eight of the patients were women and one was a man. All have been followed throughout their course and observed during various therapeutic programs. The diagnostic criteria were those outlined by Ahrens and associates.[6] In six of the nine cases surgical confirmation was obtained. In the others the clinical findings and biopsies of the liver seemed to furnish adequate support for the diagnosis.

Two patients are dead. The first died in hepatic coma following a hemorrhage from esophageal varices. The total duration of the disease in this case was about five years. The other patient who died was a man who had deep jaundice, a large liver, a blood cholesterol level of 980 mg. per cent, and a total serum lipid level of 3 gm. per cent when first seen. At earlier surgical exploration, patent bile passages had been demonstrated, and liver biopsy had been regarded as showing "cholangiolitic cirrhosis." The patient remained jaundiced and became worse. Reexploration some months later revealed a stricture of the common duct, and death followed. Dilated intrahepatic ducts were noted at necropsy. Obviously this case cannot be regarded as a classic example of primary biliary cirrhosis, but neither can the diagnosis be excluded, since the ductal stricture may have followed the earlier exploration. This case is included to indicate the necessity of surgical exploration in such cases whenever possible. Only by operative cholangiography can an obstructing ductal lesion be excluded positively. Biochemical and clinical studies unfortunately are not entirely conclusive.

Five patients (cases 1, 3, 4, 5 and 7) have received courses of steroid therapy of from 2 to 12 months' duration. Cortisone and prednisone were employed, and treatment was carried to the point of cushingoid manifestations. In general the results were disappointing, as have been those of other investigators.[14] Two patients may have derived some benefit. The one in case 7 was clinically much improved although a fracture of an osteoporotic vertebra occurred during the course of treatment. The patient in case 5 had an active rheumatoid type of arthritis which disabled her completely during the eleventh year of her disease. Steroids were used for almost one year, with good effect as far as the arthritic manifestations and general health were concerned. The pruritus, however, was never controlled. Currently there is evidence of deterioration of the liver parenchyma, and the blood lipids have diminished. She has also bled twice from esophageal varices. In case 1 the disease has remained almost entirely stationary during five years of intermittent steroid therapy.

Case 3 is of special interest and is being reported separately by the attending surgeon.[15] The patient presented herself with a classic xanthomatous type of cirrhosis and almost unbearable pruritus. Cholecystographic study revealed biliary calculi. At exploration, stones were found in the gallbladder but the common duct was freely patent and did not contain calculi. A T tube was inserted for intermittent biliary drainage. The patient has obtained complete relief from pruritus and has refused to part with the T tube (which has been replaced on one occasion). The blood lipids and bilirubin have changed little over the entire period of six years. Prednisolone given for several months on two occasions has not affected the blood lipids, bilirubin or phosphatase but has produced improvement in strength and appetite.

The possible benefits of biliary drainage in respect to pruritus were known prior to Varco's[16] report; they have been amply confirmed in this patient. There is no evidence, however, that such drainage has modified the downhill course of the disease. A correlation between blood lipid levels and the degree of pruritus cannot be shown in this case.

The patient in case 4 was the youngest in the series. The onset of the disease was insidious, with headache and fatigue. The pa-

tient had just miscarried premature twins, and the pigmentation first noted was indistinguishable from chloasma of pregnancy. There was relatively little pruritus initially. The liver and spleen were enlarged, and xanthelasma was also noted. Electrophoretic studies showed increases in beta and gamma globulins. Lipoproteins were significantly increased. Several months later the patient was seen during the third month of her second pregnancy. The alkaline phosphatase was increased (70 King-Armstrong units) but other values were little changed. The pregnancy terminated a month later. A year later cortisone was given over a two month period (from May 6 to July 15). The results are shown in table 1. Bilirubin, cholesterol and phosphatase levels fell slightly but total lipids increased. The rise in lipids was reflected in a study of lipoproteins as determined by ultracentrifugal methods (table 2). In a similar case studied by Carman and Giansiracusa,[17] a favorable effect on similarly determined lipoprotein fractions was noted along with clinical improvement. However, our patient did not benefit materially. She was examined again in 1957. Cholesterol, alkaline phosphatase and total lipids were all about 20 per cent lower than they had been a year earlier. They were not diminished further by a two month course of therapy with a linoleic acid preparation. There were no complaints except easy fatigue. There was some slight increase in pigmentation and in the size of the liver and spleen. At present the patient is about five months pregnant and is quite comfortable. Blood lipid values have not changed significantly to date. This is the second five year "stationary" case in the series; the first patient has had considerable steroid therapy, the second only the two month course.

TABLE 1

EFFECTS OF CORTISONE ON VARIOUS CONSTITUENTS OF SERUM, CHARACTERISTICALLY ELEVATED IN BILIARY CIRRHOSIS (CASE 4)*

	MAY 6	JULY 15
Bilirubin, mg. per 100 cc.	2.86	1.65
Alkaline phosphatase, units	66.4	42.0
Cholesterol, mg. per 100 cc.	514.0	386.0
Total lipids, mg. per 100 cc.	1100.0	1778.0

*Note that total lipids are unaffected.

TABLE 2

EFFECT OF CORTISONE ON LIPOPROTEINS DETERMINED BY ULTRACENTRIFUGAL TECHNICS (CASE 4)

	LIPOPROTEINS		
	SF 0-10	*10-20*	*20-100*
May 6*	418	213	587
May 28	666	342	879
July 19	497	322	677
Normal levels	283 ± 71.6	41.9 ± 20.4	40.1 ± 26.2

*Cortisone given from May 6 to July 15.

The patient in case 6 has had more consistently elevated blood lipids than any patient in the group. She has had numerous crops of xanthomas and still is greatly troubled by pruritus. She also is the only patient who has exhibited any particular tendency to generalized bleeding. A long course of linoleic acid therapy has been associated with (although it may not be the cause of) a fall in blood lipids and a modest degree of clinical improvement (table 3).

Reasons for the administration of fatty acids in these cases deserve comment. It has been known that as serum lipids fell xanthomas disappeared and pruritus was less troublesome. Diet alone has had little if any effect on lipid levels.[18] It seemed worthwhile to explore the effects of linoleic acid on these levels and to see if clinical improvement also might ensue. Gephardt,[19] incidentally, noted a sharp diminution of serum lipids while a patient with biliary cirrhosis was receiving two other fat-mobilizing substances, inositol and choline.

The patient in case 9 presented herself with ascites and esophageal varices after a three year period of jaundice, which began insidiously and without pain. Patency of the bile passages has been verified surgically and a biopsy of the liver obtained. Like the patient in case 3, she had gallstones but the patency of extrahepatic bile passages was established

TABLE 3

EFFECTS OF LINOLEIC ACID ADMINISTRATION, CASE 6

	BILIRUBIN (MG. PER 100 CC.)	ALKALINE PHOSPHATASE (UNITS)	CHOLESTEROL (MG. PER 100 CC.)	TOTAL LIPIDS (MG. PER 100 CC.)
March 1957		33	972	3021*
May 1957	4.9	33	1115	10720*
July 1957	4.2	27	1360	
Linoleic acid therapy begun				
August 1957	5.2	42	1340	15400
October 1957	5.5	32	1000	6973
November 1957		34	980	5810
December 1957		21	860	8800
January 1958	5.8		720	3952†

*Xanthomas appearing.

†Xanthomas fading.

at operation. There is now marked elevation of total lipids, bilirubin and phosphatase in the serum, but the serum cholesterol, formerly high, has fallen by 50 per cent in recent months. The patient was relieved of ascites by dietary sodium restriction and is currently improving. The presence of varices constitutes the major threat in this case.

Discussion

Little encouragement can be derived from these observations regarding the treatment of primary biliary cirrhosis. The disease still carries an ominous prognosis, although certain patients may show little evidence of deterioration over long periods. The variability in the clinical and biochemical picture as seen in this small series suggests that all cases may not have a common etiologic basis. Certainly some cases seem to carry a better prognosis for longevity than others.

Exploration of the bile passages may be recommended as essential for accurate diagnosis. Possibly a period of intermittent biliary drainage may give welcome relief from pruritus.

Use of orally administered steroids probably does not entail a special risk, contrary to the original pessimistic warning of Williams and Flink.[20,21] Linoleic acid preparations used in the hope of diminishing total lipid formation probably deserve further study. A brief experience with them, however, would indicate that they are not likely to alter the course of the disease.

ADDENDUM

Since this paper was submitted for publication, the patient in case 4 had a premature infant in the thirty-second week of pregnancy. Both mother and child are doing well. The significant thing in this case is great improvement in the biochemical pattern of the serum in the mother. Specimens obtained during the postpartum period have shown a fall in bilirubin, phosphatase and lipids to practically normal levels. How long this improvement persists will be of great interest. Parenthetically, it is unusual for a patient with biliary cirrhosis to go through a normal pregnancy.

The patient in case 5 died in coma following a severe hemorrhage from esophageal varices.

The patient in case 9 died under similar conditions. The histologic picture of the liver at autopsy was very confusing. However, it was ascertained that the bile passages were completely patent, and there seems to be no reason to change the original diagnosis.

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Postgraduate Clinical NOTES

112. MENTAL HEALTH IN OLD AGE

Old age is not a disease, it is a process. Aging is a process of decreasing strength, both physically and psychologically. It is a process of increasing limitations. It is also a social condition, involving the attitudes of people and their culture. In China the elderly formerly were held in reverence. In the United States old people are often a problem. They are not esteemed; they are shelved by industry; they often are not wanted by their children; and they are a trouble to families. Often they are sources of irritation, resentment and guilt. They are looked on not infrequently as burdens and a difficult responsibility—extra mouths to feed. Considered as economic and recreational liabilities, they are given only a grudging tolerance and are not held in veneration. It is one of the ironies of science that medicine through its scientific achievements has prolonged the length of life; yet industry, created by science, has decreed that, automatically, people should be laid on the shelf and withdrawn from activity at an arbitrarily determined age. This is one of the contradictions and schizophrenic aspects of our civilization. We have currents which run at cross purposes.

Kenneth E. Appel, Motivation in the later years of life, *Journal of the American Geriatrics Society*, March 1958, pp. 220-228

Cyanosis and dyspnea are the cardinal signs of respiratory obstruction in the newborn. Obstructions in the respiratory system include lesions in the upper respiratory tract and the pulmonary alveoli, structural deformities in the tracheobronchial tree, extrapulmonary lesions compressing the lung, and aspiration of secretions into the respiratory tract. Treatment is determined by the type of obstruction present.

Management of Respiratory Obstruction in the Newborn Period

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THE newborn infant faces one of the most critical periods in his life. He has to survive in a new environment with metabolic and physiologic processes which are untried and at times partially undeveloped. One of the most critical systems on which he must depend is the respiratory system. There is little pulmonary reserve. He barely has enough lung tissue to maintain adequate transfer of oxygen and removal of carbon dioxide. Respirations must be rapid and moderately labored. The slightest disturbance with respiratory function may prove hazardous. For this reason respiratory obstruction is extremely important to the infant's survival.

Cyanosis and dyspnea, the cardinal signs of respiratory obstruction, may result from difficulties unrelated to the respiratory tree. Two major congenital defects of the heart may cause them in the newborn period, namely, transposition of the great vessels and tricuspid atresia. Cyanosis and dyspnea also may result from birth trauma or from nontraumatic lesions of the central nervous system. All such possibilities must be considered in the differential diagnosis of respiratory obstruction.

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In the respiratory system, several varieties of obstruction may occur: (1) obstructive lesions in the upper respiratory tract, (2) structural deformities in the tracheobronchial tree, (3) lesions in the pulmonary alveoli, (4) extrapulmonary lesions compressing the lung, and (5) aspiration of secretions into the respiratory tract.

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Obstructive Lesions in the Upper Respiratory Tract

A number of lesions in the region of the nasal, oral or laryngeal pharynx may directly occlude passage of air from the atmosphere into the tracheobronchial tree. Some of the common ones are macroglossia, micrognathia, congenital laryngeal stenosis, thyroglossal cysts in the neck and tongue, and cystic hygromas in the pharynx, neck or tongue. In all these conditions one of the components of the upper respiratory tract is hypertrophied, enlarged by neoplasm, or congenitally defective. In the newborn period it may be impossible to accomplish surgical correction at once. When the problem cannot be handled in one short, effective procedure, the safest approach is tracheotomy.

Care of tracheotomy—The performance of tracheotomy does not end with opening the upper respiratory tract. Good postoperative care is imperative. This consists not only of putting in a tracheal cannula of proper size but also of providing good nursing care with sufficient aspiration whenever needed for removal of mucus and secretions. There must also be frequent stimulation to assure that the lethargic infant will clear his lungs by crying. For long-term care it is important that the tracheotomy cannula not be too long. Excessively long tubes injure the trachea and may ultimately result in tracheal stenosis, which is even more serious than the original laryngeal stenosis. In general our policy toward performance of tracheotomy follows a few simple axioms. If there is any serious question regarding the need for tracheotomy, it is done at once. However, it is always performed under the supervision of the otolaryngology department, and the patients are followed by that department until the tube is removed.

One of the commonly overlooked lesions in this group is congenital laryngeal stenosis. It can be differentiated from the others by a valuable clinical sign, i.e., the type of respiration. Infants with macroglossia, micrognathia, thyroglossal cysts, or cystic hygromas usually have loud, rough, stertorous respirations, indicating that air goes in and out of the lungs, though with some difficulty. In congenital laryngeal stenosis, in addition to absence of obvious deformity there is severe impairment in the movement of air in and out of the lungs. Auscultation reveals insignificant pulmonary ventilations, breath sounds are decreased, and the child's cry is weak because air cannot be inspired into the lungs.

Structural Deformities in the Tracheobronchial Tree

Structural deformities include both diseases within the tracheobronchial tree and lesions immediately adjacent to the trachea which can embarrass respiration by compression. The most common deformity is esophageal atresia with tracheo-esophageal fistula. It usually takes the form of a blind pouch in the upper portion of the esophagus with a fistula from the tracheal bifurcation into the lower esophageal segment. Clinically there is excessive salivation with inability to swallow without coughing or gasping. Diagnosis is made by gently attempting to pass a nasogastric catheter and noting that its passage is blocked a short distance beyond the nasopharynx. Roentgenographic confirmation is accomplished by introducing a small amount of LIPIODOL® into the blind esophageal pouch (figure 1).

Treatment of esophageal atresia requires immediate operation. A right thoracotomy is done. The tracheo-esophageal fistula is located and excised. The upper and lower segments of the esophagus are approximated with a double layer of 6-0 interrupted arterial silk sutures. If roentgenograms do not show air in the gastrointestinal tract, the esophageal pouch and the distal esophagus are extremely short; the distal esophagus is too far down to enable the surgeon to accomplish an adequate esophageal anastomosis. In this situation, since the tracheo-esophageal fistula usually is absent, esophagostomy and gastrostomy are done.

The operative mortality for esophageal atresia varies depending on the number and type of other anomalies which are rather frequently associated with this condition. Most surgical groups report an operative mortality rate of just below 50 per cent.

Another congenital lesion which may cause

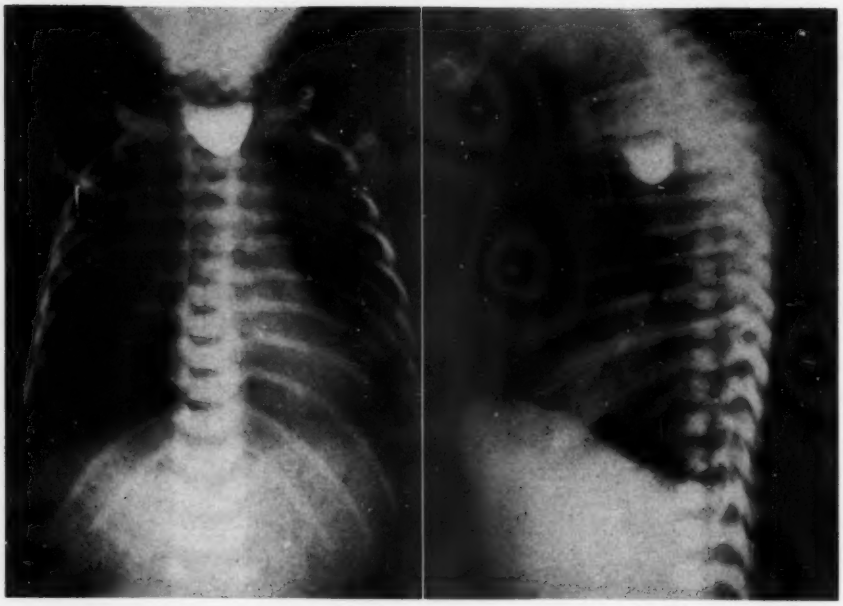
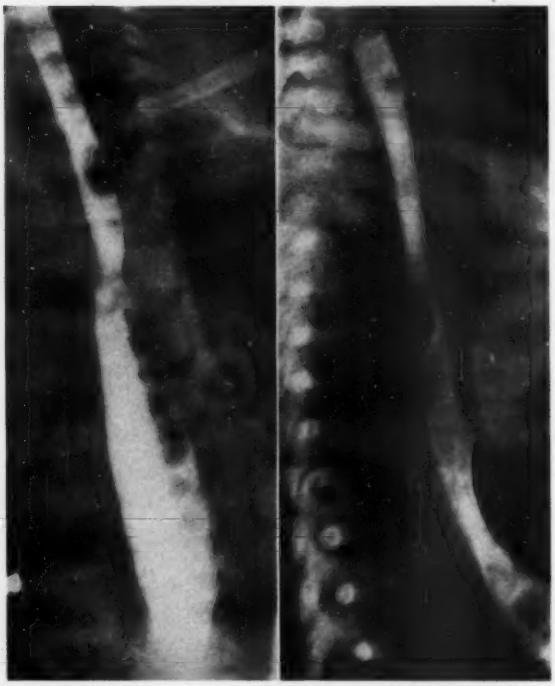


FIGURE 1. Lipiodol injected into the upper esophageal pouch to confirm the diagnosis of tracheo-esophageal fistula.

FIGURE 2. "Cooky bite" type of compression deformity in the esophagus, indicative of vascular ring.



obstruction of the tracheobronchial tree is a vascular ring. Vascular rings may be *complete*, associated with a double aortic arch, or *incomplete*, resulting from anomalous brachiocephalic vessels. In either case there is localized obstruction of the trachea and esophagus and the patient may have dyspnea or dysphagia or both. Diagnosis usually is made by means of an esophagram, which shows localized compression of the esophagus (figure 2). If respiratory obstruction or regurgitation is severe, immediate operation should be done. Operative mortality is high because endotracheal intubation is difficult and because compression of the tracheobronchial tree often results in tracheal malacia with collapse of the airway following the removal of the endotracheal tube.

This section would be incomplete without mention of diffuse infectious tracheobronchitis, which often causes respiratory obstruction in the newborn period. Although its treatment is medical, the surgeon must never overlook it in his differential diagnosis lest he inadvertently perform thoracotomy in a seriously ill infant. Diagnosis is not always easy, but the presence of fever and leukocytosis together with a history of sudden overwhelming upper

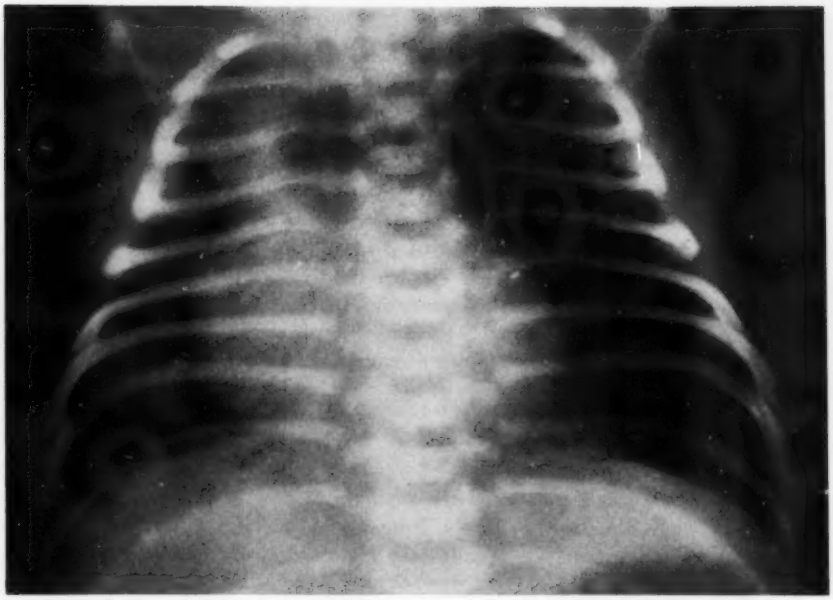


FIGURE 3. Lobar emphysema of the left upper lobe with displacement of mediastinal structures to the right.

respiratory infection and absence of signs of surgical diseases of the tracheobronchial tree are of value. Treatment consists of administration of antibiotics, placing the patient in a room which has a high moisture content, and use of any other supportive measures which might be indicated.

Lesions in the Pulmonary Alveoli

Lesions in the pulmonary alveoli causing respiratory obstruction are lobar emphysema, spontaneous pneumothorax, hyaline membrane disease, agenesis of the lung, and congenital lung cyst. In lobar emphysema there is acute distention of a segment of the pulmonary alveolar region. Air is trapped in this distended portion of the lung, and the rest of the lung is so compressed that adequate ventilation cannot occur. Treatment requires immediate thoracotomy with removal of the offending emphysematous section (figure 3).

Spontaneous pneumothorax may occur from rough instrumentation during birth or simply from ordinary birth trauma, with subsequent rupture of the pulmonary alveoli. Air accumulates in the pleural space, leading to tension pneumothorax and collapse of the lung. Some kind of decompressive instrumentation for removal of the air from the pleural space is necessary. If the spontaneous pneumothorax is mild the patient may be treated conservatively, giving the body time to absorb the air from the pleural space at its own rate. Usually, however, either thoracentesis or introduction of closed thoracotomy tube drainage is required.

Hyaline membrane disease is characterized by accumulation of hyalinelike secretions in the bronchioles and alveoli. The child usually is well at birth, but within a few hours the hyaline material accumulates. The patient becomes dyspneic and ultimately dies. This disease is found in infants born prematurely, of diabetic mothers, and by cesarean section. Some authorities believe it is associated with abnormal progesterone levels characteristically found in the blood in these three situations. However, it may not represent a metabolic disturbance at all but may be the result of localized disease within the lungs. Little is known about this condition and a great deal of work remains to be done. For the present, treatment is conservative.

Agenesis of the lung requires little comment. When it involves small areas of the total lung field the child has a chance for survival after thoracotomy and removal of the offend-

ing segment. However, when agenesis is so severe that not enough lung remains to sustain life the clinician is helpless.

Congenital lung cyst, if large enough, also may obstruct respiration in the newborn period. Diagnosis is apparent when an area of rarefaction is seen on a roentgenogram of the chest. It is almost impossible to distinguish with certainty between lobar emphysema and congenital lung cyst in the newborn. In the presence of cyanosis and localized disease, treatment of the two is the same: excision of the offending rarefied region of the lung.

Extrapulmonary Lesions Compressing the Lung

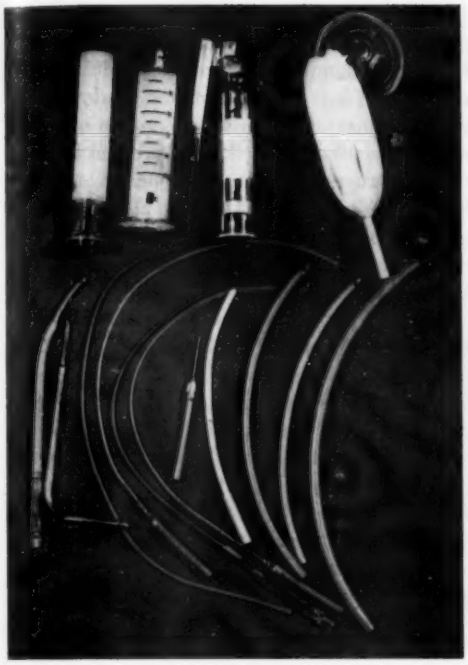
The two most common reasons for extrapulmonary compression of the lung are diaphragmatic hernia and mediastinal tumor.

FIGURE 4. Enlarged thymus casting a shadow on x-ray of the chest and causing respiratory obstruction.

These may either compress the tracheobronchial tree or collapse large segments of the lung. Treatment of mediastinal tumor in the presence of cyanosis and dyspnea is immediate surgical removal. Treatment of diaphragmatic hernia under similar conditions is correction of the hernia as promptly as possible. In treating infants, when the diaphragmatic hernia is severe enough to obstruct respiration we believe it is essential that the route of approach be abdominal rather than thoracic. It is extremely disconcerting to open the chest and find a lot of bowel which cannot be reduced into the abdominal cavity. Apparently in infancy the bowel participating in the diaphragmatic hernia has forfeited the right of domicile in the abdomen and there is no room for it to return. Accordingly there is more chance of success if the approach is through an abdominal incision. The bowel is reduced from the pleural space, the diaphragmatic hernia is repaired, and then, if there is not enough room in the peritoneal cavity to accommodate all the organs, only the skin can be closed over the bowel, thereby sealing the wound but not interfering excessively with respiration.

A number of diaphragmatic hernias will be associated with only partial development of the lung on the side of the hernia. It is easy for the surgeon to become obsessed with the idea of adequately expanding the underdeveloped lung on that side. When he urges the anesthetist to apply great pressure into the endotracheal tube, the hypoplastic lung may rupture, with subsequent pneumothorax. Even the opposite lung may rupture from excessive pressure, and the patient may die because the only good lung has been collapsed. Our policy at the Children's Hospital, whenever hypoplastic lung area is noted with diaphragmatic hernia, is to expand the hypoplastic lung as far as it will go, and seal off the pleural cavity. Within a few weeks, natural absorption of the air from the pleural space will cause adequate expansion of the lung, and in most instances the pleural cavity will be thoroughly obliterated by the time a roentgenogram is taken four to six weeks after operation.

The usual mediastinal tumor that compresses the respiratory system is some kind of tera-



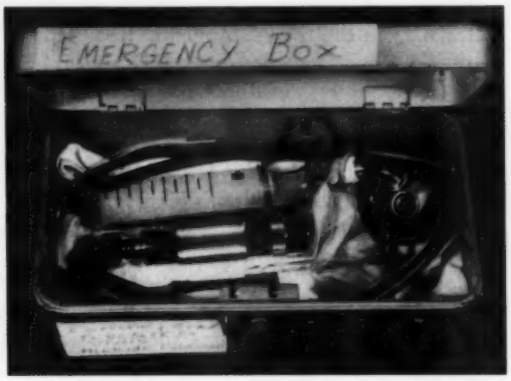


FIGURE 5. Equipment found in the emergency kit available on children's surgical wards, and method of packing the kit.

toma or dermoid cyst. Excision of this tumor is absolutely essential. The other tumor that may be present is neurofibroma or neuroblastoma. These tumors should be excised, followed by deep x-ray therapy. On only one occasion an enlarged thymus was found obstructing the respiratory tract. The thymus was removed and the patient's symptoms disappeared (figure 4). Sections of the thymus failed to reveal evidence of malignancy. This is the only instance in our experience of respiratory obstruction caused by enlarged thymus alone. At any rate, regardless of the nature and origin of the mediastinal tumor, when the respiratory tree is obstructed the offending tumor must be removed immediately to save the patient's life.

Aspiration of Secretions Into the Respiratory Tract

Any discussion of management of respiratory obstruction in infancy would be incomplete without mention of the most common cause, aspiration of oral or enteric secretions which have been regurgitated into the pharynx. There are two situations in which this most commonly occurs.

1. Immediately after birth the child, as it is being delivered, may aspirate amniotic fluid, oral secretions and possibly enteric secretions, with subsequent atelectasis. Because this is such a common occurrence, obstetricians are very much aware of it, and so are pediatricians. Aspiration of the tracheobronchial tree is practiced routinely during resuscitation of the newborn.

2. Of even greater importance is the fact that aspiration of regurgitated oral or enteric material is one of the most common causes of postoperative death in the newborn period. Any hospital with adequate surgical facilities for operations on newborn infants must assume that this accident may often occur without warning. The whole medical and nursing staff must be geared to its efficient and effective management. To this end, all newborn infants should be taken to a pediatric recovery room after operation, where there are special-

ly trained personnel who are aware of the necessity for maintaining an adequate airway and who can recognize respiratory obstruction quickly and correct it rapidly.

In addition, there should be available on the wards emergency kits which have laryngoscopes, endotracheal tubes, aspiration catheters and equipment for administering oxygen. Residents and attending staff must all be skilled in the introduction of soft endotracheal catheters and proper technic for removing material from the tracheobronchial tree. This is often a lifesaving procedure. When aspiration occurs, the responsibility for clearing the respiratory tree falls squarely on whoever happens to be immediately available. There is no time for consultation. Delay is fatal.

In general, at the Children's Memorial Hospital, the operative unit consists of the usual kind of operating room with all its efficiency. It is supplemented, however, with a recovery room in which the patient remains for the first four to six hours, until he has adequately recovered from anesthesia. It is also supplemented by an intensive postoperative therapy unit manned at all times by adequate nursing personnel, where the children are placed a few to a room. There are available oxygen, emergency kits, laryngoscopes, endotracheal tubes, respirators, incubators, and so on, all of which are used to correct or prevent respiratory obstruction during postoperative convalescence. This is provided for all patients regardless of financial status. It has been one of the most significant factors in reducing operative mortality (figure 5).

Another important factor in reducing operative mortality has been the adoption of feeding by dropper in cases of very weak newborn infants, who obviously cannot feed from nipples. The attending nurse is trained to feed the infant slowly, drop by drop, carefully introducing the vitally needed calories and fluids. Although this method is time-consuming, it eliminates the danger of aspiration associated with nipple feeding. Operative mortality in tracheo-esophageal fistula, intestinal obstruction in the newborn, and all operative procedures in premature infants would be much higher were it not for this method of feeding.

Postgraduate Clinical NOTES

113. EMOTIONAL PYREXIA

Peculiar to children in their *school years*, though by no means confined to this age range, are fevers of emotional or functional origin. The adjective "highly strung" has suffered such inflation in recent years that one hesitates to use it, and yet a child of this type will be recognized as one who often develops fever as the result of emotional tension. Some such children sometimes show a regular temperature of 99° F. (37.2° C.) or so in the evenings for weeks on end. More phlegmatic children, too, may "run a temperature" on the eve of a birthday or on the last day of the holidays. A normal blood sedimentation rate may rarely be misleading, but in the main this is a valuable means of distinguishing between emotional fever and cryptic infection.

R. M. Mayon-White, The pyrexial child, *Practitioner*, March 1958, pp. 298-304

The development of new ocular medications has led to great changes in ocular therapeutics, and to the virtual disappearance of some previously common ocular diseases. However, these same drugs have led to a whole new series of diseases. The author emphasizes the need for physicians to know the value of the drugs available, as well as their limitations and the complications they may cause.

THE SCHNEIDER FOUNDATION EYE PRESENTATION

Drugs Effectively Used in Problems of the Eye

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THE Schneider Eye Research Foundation Lecture, probably the first such presentation in this country to be devoted to the field of ophthalmology, has been given at each annual Assembly of the Interstate Postgraduate Medical Association since 1925. Although Dr. Schneider died in 1927, his spirit of inquiry, his surgical skill and his humanity are still remembered by professional associates and patients. The lectures sponsored by his gift have included a broad range of subjects pertaining to constitutional diseases and their relationship to the eye. I feel greatly honored to have been invited to give this thirty-fourth Schneider Foundation Lecture.

The past two decades have witnessed a revolution in ocular therapeutics with the development of the sulfonamides, antibiotics, steroids and new drugs affecting the autonomic nervous system. A number of previously common ocular diseases have almost disappeared. It is uncommon nowadays for the ophthalmologist to see an acute case of conjunctivitis of bacterial origin. Trachoma can be cured; the causative virus has been identified and its elimination is a public health problem. The steroids have proved effective in some cases of uveitis, and in many groups the time-honored foreign-protein fever therapy is no longer used.

With the advent of these new drugs and the elimination of ancient scourges a whole new series of diseases has emerged. More and more, it is being recognized that in the therapy of eye diseases, as in other fields, many

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of the new drugs are double-edged swords. They must be used with understanding and competence. Unwise empirical use may lead to a more serious condition than the one the physician is attempting to cure.

The classes of drugs which can be used effectively and which are indicated in problems of the eye are surprisingly limited. This is not to say that the number of such drugs is small; a large variety of ocular medications are released commercially at frequent intervals. However, many of these new products have no medical reason for their distribution, and a physician would do well to limit himself to compounds he has used previously with satisfactory results. Parenthetically, there are a few ancient remedies which have been traditionally used in ophthalmology and probably may be discarded. This group includes the silver proteinate solutions, the yellow oxide of mercury ointments, quinine bisulfite, and probably the ammoniated mercury compounds, although these have limited use on occasion.

Antimicrobial and Chemotherapeutic Compounds

There are several antimicrobial agents and chemotherapeutic compounds which are of unusual value in the treatment of superficial inflammations of the conjunctiva. NEOSPORIN®, a mixture of neomycin sulfate, polymyxin and gramicidin, is an unusually valuable compound to use locally. It has a wide bacterial spectrum and contains antibiotics which rarely will be used systemically, so the production of local hypersensitivity reaction will not prejudice further therapy.

Another antibiotic which may be used with value locally is chloramphenicol (CHLOROMYCETIN®). It has a wide range of activity against both gram-negative and gram-positive organisms. Usually its use is indicated when Neosporin has been ineffective.

The decision to use a particular compound is based on the organism found by culture at the time the patient is first seen. However, culture of the causative organism in conjunctivitis is seldom done outside of institutional practice where the facilities are easily available. Empirical therapy of conjunctivitis obscures the cause of many ocular infections; a condition which may have been specifically treated in its early stages becomes an obscure, chronic inflammatory problem because it has been treated with a whole range of compounds.

The tetracyclines (ACHROMYCIN®, TERRAMYCIN®, AUREOMYCIN®) are so widely used systemically that they probably should only rarely be employed locally, again because of the dangers of a hypersensitivity reaction. This, however, is fairly uncommon and is not too serious a problem.

Other antibiotics which may be used effectively include bacitracin, which has a limited action against gram-positive organisms; erythromycin, which may be effective against organisms resistant to other compounds; and polymyxin B sulfate, which is effective largely against gram-negative organisms. Use of the latter agent is reserved for the most part for treatment of inflammations arising from *Pseudomonas aeruginosa*.

The sulfonamides are not used as extensively as they were formerly, but nonetheless are extremely valuable drugs, being of low cost and low antigenicity with a wide bacterial spectrum. The two sulfonamides which I believe are most valuable are sulfacetamide sodium (SODIUM SULAMYD®) and sulfisoxazole (GANTRISIN®).

When these drugs are prescribed in the treatment of bacterial conjunctivitis they should be instilled in the conjunctival sac frequently, every hour or two being the most effective schedule. The conjunctival sac will hold only a single drop of medication. The excess overflows, and therefore one need not be concerned about harmful results from instilling more than a single drop of solution.

If there is a great deal of secretion, an ointment may be used at bedtime to prevent adherence of the lids. I believe this is the only indication for the use of topical ointments in the eye.

There are several drugs which should never be used topically because of the possibility of hypersensitivity reactions of the conjunctiva and the skin of the lids. The most common offender is penicillin. Streptomycin is more antigenic but fortunately is used much less

commonly. Sulfathiazole was a frequent offender in years past and should never be used locally.

The compounds recommended for use should not be combined with cortisone, hydrocortisone or any other steroid. The effects of antibiotics on the bowel in causing an overgrowth of fungi because of destruction of normal bacterial flora are well known. In recent years destructive fungal infections of the cornea have been observed following the use of antibiotics combined with steroids. Usually these follow a relatively minor superficial abrasion of the cornea, commonly caused by a twig, and a deep corneal inflammation from a fungus develops. Experimentally such inflammation cannot be produced except when the antibiotic is combined with a steroid, but many authorities suggest that the antibiotic solely may cause this tragedy.

Local Anesthetics

A local anesthetic is essential in removing foreign bodies from the cornea and also may be used in differential diagnosis of ocular pain. A topical anesthetic completely relieves the pain arising from a foreign body but does not affect the pain of acute glaucoma or iritis.

The most valuable local anesthetic available is tetracaine hydrochloride (PONTOCAINE®) in a concentration of 0.5 per cent. It has the disadvantage of causing stinging, conjunctival injection, and a very minute breakdown in the corneal epithelium. Use of benoxinate hydrochloride (DORSACAINE®) avoids many of these difficulties, but it has been used for less than five years and is not as well known as tetracaine hydrochloride. These anesthetics are extremely likely to cause hypersensitivity reactions of the skin and conjunctiva. They should never be prescribed to relieve the pain following removal of a foreign body, for in addition to their antigenic properties they delay corneal healing. One may minimize the discomfort which follows removal of a corneal foreign body by using a tight pressure dressing, holding the lids closed over the eye, and by administering salicylates systemically.

A complication arising from the use of tetracaine hydrochloride which recently has been recognized is its contamination with APC virus, causing epidemic keratoconjunctivitis. Except for this organism the solution is largely self-sterilizing. However, epidemic keratoconjunctivitis is such a serious disease that considerable care is necessary to prevent contamination of the dropper. If the drug is used frequently, separate droppers are recommended. At our institution we have thus far avoided difficulty by limiting the amount of solution in a bottle to 5 cc. and discarding the unused solution each week. Another danger arising from local anesthetics is the possibility of injury to the eye while the cornea and conjunctiva are anesthetized. This is a minor danger unless the drug is prescribed for home use to relieve ocular pain.

Cocaine hydrochloride in 0.5, 2, 4 and 10 per cent solutions is still the standard of comparison for all other local anesthetic agents. However, it causes dilation of the pupil and, more importantly, causes desiccation of the corneal epithelium, which may be removed with ease after the instillation of cocaine. Because of this and because it results rarely in stimulation of the nervous system it has fallen into disfavor in recent years.

Dyes

Diagnosis of corneal foreign bodies in areas of corneal epithelial abrasion is greatly aided by the instillation of a vital dye such as fluorescein in a 2 per cent alkaline solution. Areas in which the corneal epithelium is not intact stain a brilliant green. The great disadvantage of fluorescein is that it frequently becomes contaminated with *Ps. aeruginosa*, an organism largely without pathogenic significance except when introduced into the genitourinary system or the abraded corneal epithelium in the eye, where it causes a necrotizing keratitis that may destroy the eye in 48 hours. Because of the frequency with which fluorescein is contaminated, it must be used only in a sterile solution for single instillation; alternatively, the fluorescein paper strips may be used. It must never be used from the usual multiple-dose eye dropper bottle in treating a number of patients.

Merbromin (MERCUROCHROME®), 2 per

cent, is a moderately useful substitute for fluorescein but does not stain as effectively. It has the advantage, however, of being less likely to become contaminated.

Autonomic Drugs

A host of autonomic drugs are used in treatment of glaucoma, iritis and similar diseases. Frequently these diseases present problems of differential diagnosis which require all the skill and ophthalmic equipment possible to establish their identity. For this reason, unless one has slit-lamp magnification and a tonometer to measure intraocular pressure I would not suggest that he use autonomic drugs such as atropine, scopolamine, homatropine, etc.

Atropine is effective for 14 to 21 days after local instillation and should not be used except in a few limited conditions. It is urged that phenylephrine hydrochloride (NEO-SYNEPHRINE®) in a 2.5 per cent solution be used routinely in physical examinations to dilate pupils for ophthalmoscopic examination. There is no danger in this dilation, even in patients with glaucoma, provided the pupils are always constricted before the patient leaves the office. Pilocarpine hydrochloride, 2 per cent, is effective in neutralizing the effect of this dilation.

Epinephrine hydrochloride (ADRENALIN®), 1 to 1000, is of moderate value in causing vasoconstriction of the conjunctival blood vessels and in aiding in the differential diagnosis of the cause of an inflamed red eye. If the blood vessels are constricted with 1 to 1000 epinephrine, conjunctival injection only is present and the disease probably is minor. Ciliary congestion associated with keratitis, iritis and angle-closure glaucoma is not affected by the drug. Epinephrine additionally has a limited use in preventing burning and itching of the eyes from hay fever, vernal conjunctivitis and hypersensitivity reaction. When used for a long time it may cause pigmentation of the margins of the eyelid, giving an appearance of excessive mascara on the lids.

Steroids

The steroids may be used effectively in inflammations of the sclera, in vernal conjunctivitis, in nongranulomatous iritis, and in some cases of granulomatous iritis. However, it is recognized that steroids may cause or at least encourage a number of serious ocular diseases. In herpes simplex keratitis, which in years past was a relatively self-limited although painful disease, the unwise use of steroids has caused the condition to become a major factor in a disabling ocular inflammation. The steroids reduce local tissue immunity and cause the virus to spread through the cornea and even to invade stromal layers, although ordinarily the virus is confined to the epithelium. On occasion this has resulted in perforation of the globe with loss of intraocular contents. Steroids also suppress the proliferation of fibroplastic tissue and, following ocular lacerations, may prevent the healing of apposed surfaces. As noted previously, when combined with antibiotics they may allow the proliferation of fungi within the tissues. Generally, therefore, their use should be restricted to those conditions in which they are indicated, and they should not be used empirically.

Irrigating Solutions

A wide variety of compounds have been recommended for irrigation of the eyes, ranging from mercuric oxycyanide solutions and ZEPHIRAN® to various buffers such as bicarbonate, phosphate buffer and citric acid solutions. In treatment of chemical burns of the eye it should be emphasized that whether the causative agent is acid or alkaline there is no better first-aid treatment than copious immediate irrigation with water. There should be no delay to seek the appropriate neutralizing solution; rather, as much of the compound as possible should be removed from the eye as early as possible by plain tap water.

A use of normal saline which is not widely known is in the removal of corneal foreign bodies. A foreign body *on the cornea* can be removed only after the eye is completely anesthetized. If symptoms point to a corneal foreign body and none can be seen, a drop of fluorescein frequently will delineate the area as a brilliant green patch with the dark foreign body in the center. The easiest way to remove the foreign body is with an ophthalmic syringe which directs a fine stream of water at the cor-

nea and floats out the particle. A similar technic can be employed using a small hypodermic syringe, but this is not as effective. Approximately 40 per cent of all corneal foreign bodies seen industrially can be floated out completely in this manner without danger of further injury to the eye. An even higher percentage of foreign bodies which are not hot when they strike the eye can be removed by irrigation in this manner.

Ointments

Ointments have the advantages of prolonged contact with the eye and gradual release of medication. They have a severe drawback, however, in becoming incarcerated in healing corneal epithelium and causing a recurrent corneal abrasion. Additionally, in inflammation of the lid they may become incarcerated in a necrotic area and cause a chronic lipid granuloma. For this reason the use of ointments should be limited to patients with conjunctivitis to prevent agglutination of the lids during the night.

Corneal Healing

Many of the medications used locally delay corneal epithelization. None is known which accelerates the growth of corneal epithelium. Local anesthetics and sulfonamides are the most widely known offenders in this respect. It is wise, therefore, to limit medication to the period required or to use no medication at all if it is not definitely indicated, as the natural defenses of the eye usually are adequate to permit uncomplicated healing.

It is wise, too, to recognize that a compound is not without potential danger to the eye merely because it is sold in a dropper bottle or an ointment tube. The antibiotics, sulfonamides and local anesthetics all may give rise to sensitivity reactions. Even though they are effective against many organisms, their spectrum may be such that they are contaminated with other organisms once the container is opened. Fortunately, in recent years the interstate shipment of nonsterile ophthalmic preparations has been prohibited, but intrastate or local shipment is not affected by this ruling. In addition, once the container is opened contamination is likely.

Antihistamines should not be used locally, since they are frequently prescribed for patients who already are hypersensitive to a host of substances and are likely to become sensitive to the locally applied medication also. Steroids are associated with a number of complications, and their use should be severely restricted to the serious conditions in which they are effective.

Epilepsy is best studied as a symptom of brain disease rather than as a disease in itself. The diagnosis of the seizure depends on witnessing an attack or obtaining an adequate history of such seizures. For proper handling of causes, social management and treatment of the patient, it is useful to classify the seizure by its clinical symptoms and to describe it as grand mal, petit mal or focal. Therapy is aimed at control of seizures, and may be achieved by psychologic, medical, dietary and surgical methods.

Treatment of Epilepsy

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EPILEPSY is a common and dramatic symptom of brain disease. An epileptic seizure is a symptom of disturbed cerebral function and as such may be manifested by any of the physical or psychologic accompaniments of cerebral activity. Thus the epileptic attack may include every feeling or movement of the patient in infinite variety. A seizure may be defined as a brief, paroxysmal, stereotyped cerebral storm inappropriate to the immediate situation and followed by transient impairment of cerebral function.[1] Repetition of attacks is usually regarded as essential in the diagnosis of epilepsy.

These symptoms (seizures) may be induced in anyone by alterations in cerebral physiology. The ease with which seizures may be produced is variable. In the young child seizures may be precipitated more easily than in the adult. There is a variation in susceptibility in patients of the same age and even in the same patient from time to time.

Epilepsy is best studied as a symptom rather than as a disease. To the patient and his relatives, this symptom is a catastrophic event, and the diagnosis alone may mean loss of social prestige and financial security. To the clinician, this symptom is often an important sign of more serious brain disease, the diagnosis of which will require all of his scientific acumen. Treatment of the symptom requires his utmost skill in the art and the science of medicine.

The diagnosis of the epileptic seizure depends on witnessing an attack or obtaining an adequate history of such seizures. Laboratory tests such as the electroencephalogram may confirm such a diagnosis, but the diagnosis itself depends on the presence or absence of the clinical symptom.

Once the diagnosis of epilepsy is deter-

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mined, the physician may plan his strategy of treatment. This consists for the most part of three phases: (1) The causes of the convulsive disorder must be recognized and eradicated when possible. (2) When eradication of the cause is not possible, the patient must be instructed in how to live with his illness. (3) Medical treatment for the epileptic symptom must be prescribed.

Classification

For proper handling of the causes, social management and treatment of the patient with epilepsy some method of classifying the disorder is essential. We have found it most useful to classify the epileptic seizure by its clinical symptoms. In this way epileptic seizures may be described as grand mal, petit mal or focal.[2]

Grand mal—Grand mal seizures are those which are universally recognized as epileptic seizures. The attack begins with unconsciousness and a tonic contraction of the body musculature. The eyes roll upward, the legs are extended, and the arms are flexed. The force of the muscular contraction causes forced expiration of air from the lungs. The tongue is frequently caught between the teeth. The bladder and bowel may be emptied involuntarily. The patient falls forcefully to the ground. The tonic stage persists for a few seconds to half a minute, and during it the patient may become cyanotic. The clonic convulsive stage then begins, and the body and extremities jerk and twitch. After a few minutes the muscles relax, the patient regains partial consciousness, and his color improves. At that time he is somewhat confused, complains of headache and of muscular pain, and generally falls into a deep sleep.

Grand mal seizures are often the final common event of any epileptic attack. Thus, spread of the epileptic discharges underlying either the petit mal or the focal seizures may result in a grand mal seizure.

Petit mal—Petit mal seizures are those seizures of childhood which consist of transient lapses of consciousness associated with three per second spike and wave discharges in the electroencephalogram. These attacks last only a few seconds but recur often, sometimes many times daily, if no treatment is given. The attack itself consists of sudden loss of consciousness with the patient appearing to stare into space, and there may be twitching movements about the eyelids, face and sometimes the upper extremities. The patient is mentally clear up to the onset of the seizure and appears normally alert when it ends. Occasionally attacks of petit mal may be followed by a grand mal seizure.

Focal seizures—Focal seizures are those epileptic attacks whose initial clinical symptoms suggest irritation of a discrete area of the brain. At times these seizures may spread to become grand mal attacks. We have found it useful to divide all focal seizures into two broad categories. The first type we have called "splanchnopsychic seizures."[2] This term includes all seizures initiated with complex hallucinations, perceptual or conceptual illusions, affective states, and various autonomic phenomena involving the cardiovascular system, the abdominal viscera, respiration (in short what we have previously described as "visceral seizures"),[3] and may terminate in confusional states (automatisms) or generalized convulsions. In general this category consists of what previously have been called "temporal lobe" or "psychomotor" seizures.[4] We chose a behavioral term for these seizures because the so-called temporal lobe seizures are not invariably associated with temporal lobe lesions and the term psychomotor did not seem to stress sufficiently the frequent visceral symptomatology. The remaining category of focal seizures that we use, namely, the "sensory-motor seizures," includes all focal somatomotor seizures (jacksonian seizures), so-called supplemental motor area seizures, adversive seizures and crude somatosensory and visuosensory seizures (table 1).

Etiology

Epilepsy is a symptom, and each epileptic seizure is the result of multiple causes. Certain morbid states of the brain give rise to epileptic seizures as one of their characteristic symptoms. The recognition and differentiation of these specific causes are of importance in the

TABLE 1

TYPES OF SEIZURES AND CAUSE OF EPILEPSY AS SEEN IN 1284 PATIENTS[2]

TYPES OF SEIZURES	PER CENT OF CASES	CAUSE	PER CENT OF CASES
Nonfocal		Brain neoplasms	10
Grand mal	36		
Petit mal	11		
Focal	44	Atrophic lesions	18
Unclassified	9	Unknown	72

proper treatment and diagnosis of epileptic disorders.

Heredity—Heredity is commonly assumed by the patient, his family and, frequently, his physician as being the chief cause of his epileptic attacks. Many patients and their families arrive at their physician's office with elaborate documentation of the hereditary "causes" of the patient's seizures. Just as frequently other patients and their families arrive with equally vehement denials that any such symptoms have occurred in their family.

The exact degree to which heredity or genetic factors influence the development of seizures remains controversial. Alström,[5] after a careful study of 897 families with epilepsy, concluded that the incidence of this disorder among the close relatives of epileptics did not significantly exceed that of the general population. Our experience is similar to that described by Lennox.[6] A family history of seizures is obtained in about 10 per cent of our patients with epileptic disorders regardless of type or cause. This suggests that, although a predisposition or predilection to an epileptic disorder is inherited, in most instances an additional cerebral morbid state is needed to initiate the disorder. If certain inherited neurologic syndromes of which epilepsy is only a symptom are excluded from consideration, epileptic disorders appear to be inherited less frequently than many other common diseases.

Organic diseases of the brain—A number of brain lesions are recognized in which epileptic seizures are frequent and occasionally initial symptoms. These can be distinguished for the purpose of treatment into mass lesions such as tumors and atrophic lesions in which there is primarily a loss of brain substance, as, for example, in cerebral thrombosis. The variable prognosis and therapy of these disorders necessitate their recognition.[2]

Atrophic lesions of the brain—Epilepsy with loss of brain substance is most common in the epileptic seizures which begin at both extremes of life. Perhaps the most common cause for these is trauma. Cerebral vascular disease in spite of its frequency does not account for a large percentage of the epileptic disorders. It is true that an acute infarct or cerebral hemorrhage may be accompanied by an epileptic attack. The cerebral ischemia associated with transient arterial insufficiencies also may be associated at times with an epileptic seizure. In certain patients with focal cortical infarcts, epileptic seizures may be a late sequela.

Epileptic seizures may occur frequently during an acute infection of the brain. This is particularly true in patients with encephalitis. Epilepsy may occur as a late sequela of infections which directly involve the cortex. In a wide variety of other illnesses affecting the central nervous system, epileptic seizures may play an important symptomatic role. These include such entities as tuberous sclerosis, Alzheimer's disease, Sturge-Weber syndrome and, rarely, multiple sclerosis. It may be safely assumed that any disease of the brain may be accompanied by an epileptic disorder at times.

Brain tumors—Brain tumors are commonly associated with convulsive disorders. In our experience 10 per cent of the patients with epilepsy seen in an outpatient clinic have brain tumors.[2] It is of particular importance for the physician to recognize these patients, because surgical removal of the tumor is the treatment of choice in most instances.

We have observed that the following clinical criteria suggest to the physician that further diagnostic studies to eliminate brain tumor are required in patients with epileptic seizures: (1) Onset of the seizures is between the ages of 30 and 60 years. (2) The epileptic seizures are focal in type. (3) The duration of the illness is less than five years.

The following clinical criteria suggest that brain tumors need not be seriously considered as the cause of the epileptic seizures: (1) Onset of epilepsy is before the age of 20 years and the skull is roentgenographically normal. (2) The epileptic seizures are of the petit mal type. (3) The duration of illness is more than 10 years.

Diagnostic measures which are of value in determining whether or not a patient has a brain tumor include the neurologic examination with careful funduscopic examination, plain roentgenograms of the skull, and electroencephalograms. These should be a portion of the study of all patients with convulsive disorders. If they give negative results, it is permissible to assume for the moment that there is no tumor in patients whose seizures began before the age of 20 years. Obviously, all patients must be re-evaluated periodically.

In patients with focal seizures beginning in adult life, a structural lesion, possibly a tumor, must be assumed to exist. Failure to demonstrate such a lesion by additional tests such as angiography and pneumoencephalography does not preclude existence of a tumor, and the patient must be carefully re-examined at regular intervals. In such a patient the additional finding of a focal abnormality in the electroencephalogram, focal neurologic signs, or evidence of focal changes in the roentgenograms of the skull increases the level of suspicion and in certain patients may enable the physician to make a definitive diagnosis.

Metabolic disorders—It is generally taught that disturbances in metabolism may account for convulsive disorders, particularly those disturbances involving blood sugar and calcium. Recognizable disturbances in metabolism, however, account for a very small percentage of the epileptic patients seen, less than 0.1 per cent.

It is true that hyperinsulinism may precipitate convulsive disorders and that this "epilepsy" may be cured by removal of a functioning adenoma of the pancreas. Usually this diagnosis is made on the basis of the history and confirmed by the finding of low levels of blood sugar during or immediately preceding a convulsion. Routine use of tests of fasting blood sugar for every epileptic patient, however, does not seem a particularly successful or economical method of screening for this uncommon disorder. In addition many epileptic attacks are precipitated during periods of relative hypoglycemia. The seizures, however, do not respond to treatment of the relative hypoglycemia.

Hypocalcemia is another rare cause of convulsive disorders which may be most difficult to recognize. In most instances, the diagnosis can be made only by the finding of a low concentration of calcium in the blood during that patient's symptoms.

Systemic diseases—Many systemic illnesses, such as uremia and disturbances in cardiac output, may be associated with convulsive disorders. In our experience the convulsion is only a relatively unimportant manifestation of the systemic disease. Therefore, we shall not discuss this group of patients.

Febrile convulsions—Convulsions with abnormal elevation of temperature are frequent in the infant or young child. Moreover, seizures due to other seemingly trivial causes may occur in infancy. Thus, the occurrence of epileptic seizures in infants secondary to recognized illness need not be regarded as the beginning of an epileptic disorder.[7] According to Thom,[8] about 8 per cent of children have febrile convulsions, and 12 per cent of those with febrile convulsions have epileptic seizures later in life. Although febrile convulsions may be the initial symptom of an epileptic disorder, in most instances they seem to be a benign disorder. If febrile convulsions recur, the patient should be given anticonvulsant medication.

Orienting the Patient

When the diagnosis of epilepsy has been established and no "cause" for the seizures has been recognized, it is customary to diag-

nose the epileptic disorder as essential or idiopathic epilepsy. Perhaps it would be better to classify it as "epilepsy of unknown cause." In idiopathic epilepsy the social aspects of the disease are often far more handicapping than the illness itself. A peculiarly vicious wealth of half-truths, misinformation and folk tales about this disorder has been part of our culture for thousands of years. In 400 B.C. Hippocrates attempted to correct some of this misinformation in his classic essay on the sacred disease in which he described epilepsy as a disease like other diseases.[9] Even today it is incumbent on the physician not only to provide information about the epileptic disorder but also to correct some of the popular misconceptions about the illness itself prior to instituting medical therapy.

The patient and his family will be most concerned about the prognosis of epilepsy and the limitations this disease imposes on the patient. Often prior to discussing these questions, it is necessary to discuss briefly the specific eponym which is to be given to the diagnosis. Often in an effort to avoid the term "epilepsy," the term "convulsive disorder" has been used, and frequently an attempt has been made to use other terms to avoid the connotations of the older term. Regardless of the term used, it is best to discuss frankly with the patient and his family the interrelations of these diagnoses so that a later physician does not inadvertently cause alarm and distrust by the use of another diagnostic term.

Prognosis—In discussing prognosis, the physician will need to describe in general terms the clinical course of the epilepsies. Those patients who have an underlying cerebral lesion will follow the clinical course of their basic illness, whether this is a brain tumor, a vascular infarct or other disease of the brain. When the cause is not known, the clinical course is variable. Most of the data on the clinical course of idiopathic epilepsy have been obtained from patients in epileptic colonies or from large epileptic clinics. These patients obviously are selected groups and in our opinion are not comparable to the average epileptic patient seen in the physician's office. The data that we will use include our

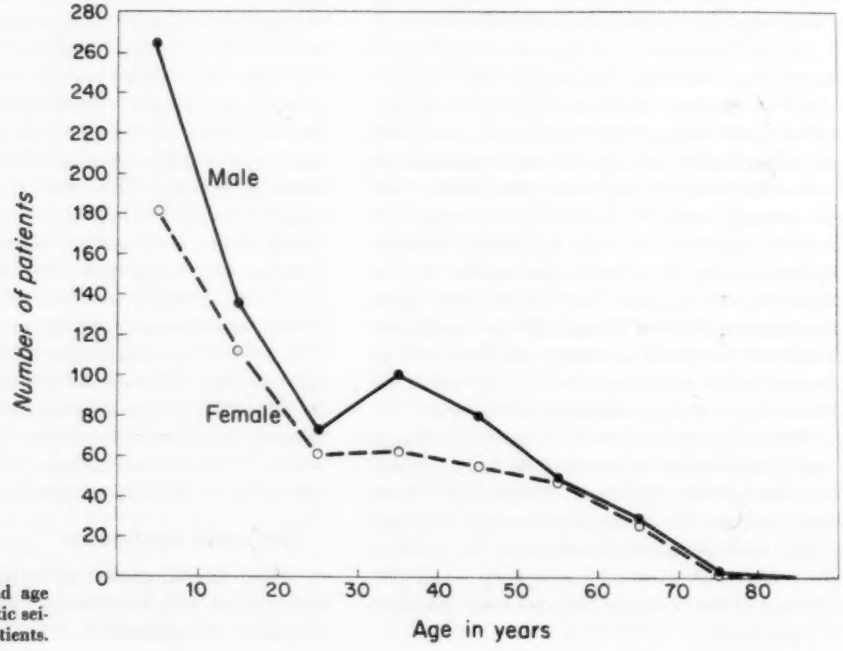

FIGURE 1. Sex and age at onset of epileptic seizures in 1,284 patients.

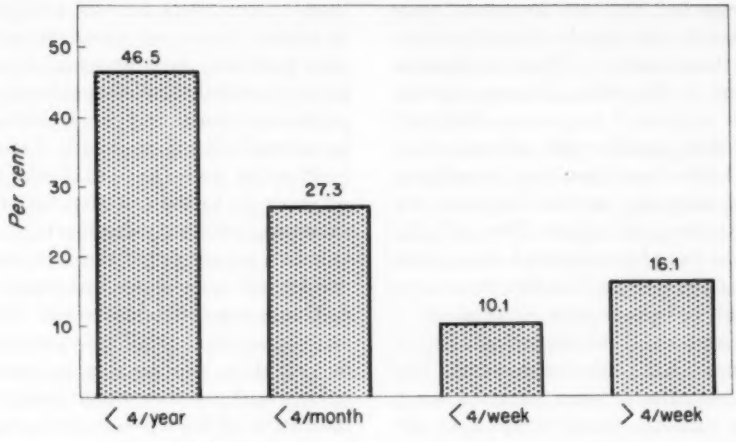

FIGURE 2. Frequency of convulsions in 1,232 epileptic patients.

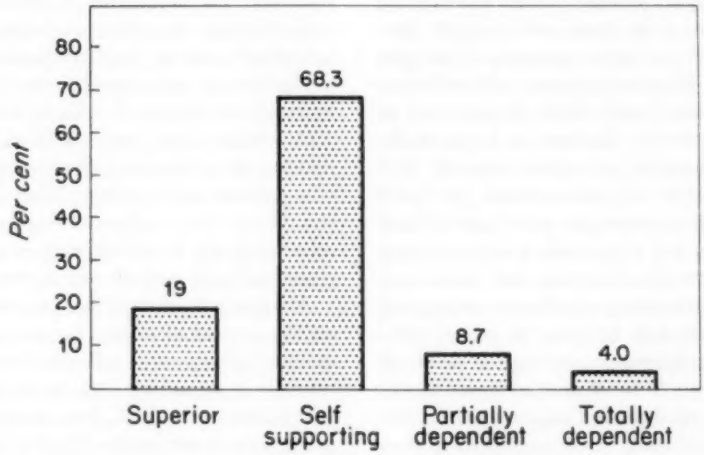

FIGURE 3. Social adjustment of 1,235 epileptic patients.

experience with 1,284 consecutive patients seen at the Mayo Clinic in 1954[2] (figure 1).

Epileptic seizures tend to begin early in life and are more common in the male than in the female. Of great importance to the patient and his family are the questions relating to the prognosis of his illness. These questions usually include queries regarding the frequency of convulsions, the hope, if any, of remissions, the efficacy of treatment, and the probable effect on the patient's social adjustment.

The frequency of convulsions varies greatly. Many patients have few convulsions in a lifetime, and about a half of our patients have less than four convulsions a year. Convulsions tend to be more frequent in the first year of life and again in adolescence (figure 2).

Remissions—In our experience, it is not uncommon for patients with epileptic disorders to have a complete and apparently permanent remission. The remission rate is not necessarily dependent on the use of modern medication, for carefully documented reports of complete and long-maintained remissions

in patients who had epilepsy for many years appeared prior to the introduction of modern methods of treatment.[10,11] These remissions not only occur in idiopathic epilepsy but also occur in that secondary to trauma. Walker[12] has reported that patients with infrequent attacks have a higher remission rate. In patients placed on an adequate medical regimen, the remission rate is much higher. The epileptic seizures can be completely controlled in about 50 per cent of the patients; in the remainder, the attacks can be appreciably diminished.[13]

Social adjustment—Epileptic seizures have always stigmatized the affected patients. The patient with seizures is often shunned, and, therefore, he and his family may hide the symptoms. His opportunities in work and social life are limited. The frequent chronic disability of epileptic patients is well known, and the presence in most states of separate state institutions for epileptic patients highlights this disability. In our experience with epileptic patients we have found that 13 per cent of them are sufficiently disabled to be partially or totally dependent on others socially and economically. On the other hand, included among epileptic patients are many individuals (19 per cent in our experience) who continue to make a superior economic and social adjustment. In determining whether or not a given epileptic patient will be able to make satisfactory social adjustment, the age at onset of the disease seems to be of crucial significance. If the convulsive disorder began prior to the age of 10 years, and, more specifically, if it began in the first year of life, the patient's adjustment is uniformly poor.[14] However, this adjustment does not seem particularly altered by the type, frequency or duration of the epilepsy. It has seemed to us that the frequent poor social adjustment of the epileptic patient is related to brain damage which is the cause of the epileptic disorder rather than to the epilepsy itself. In our experience many epileptic patients lead natural, normal lives in school, at home and at work (figure 3).

Restrictions—The patient and his family are vitally concerned with the restrictions that must be placed on him. Not only are there medical restrictions for the patient, but in many states there are, in addition, legal restrictions. The most common one has to do with marriage. It is necessary to tell the epileptic patient that no clear answer can be given at present concerning the problem of heredity in epilepsy. Some authorities, after extensive and careful study, have suggested that there is no evidence to indicate that heredity plays an important role in the causation of epilepsy. Others have suggested that heredity does play a role, but not a more important one than it does in many common diseases. The physician can suggest to the epileptic patient that his or her children will have a greater chance of having epilepsy than other children. Further, the chance of the children having epilepsy will be diminished by marrying a person with no familial history of epilepsy and presumably by marrying one with a normal electroencephalogram. In our experience, as we have previously noted, the hereditary factor plays a significant role whether the cause of the epileptic disorder is known or unknown.

A similar legal and social taboo involves driving. It is the duty of the physician to advise patients with epileptic disorders that they should not drive automobiles or engage in any other activity in which they may be injured while epileptic attacks are uncontrolled.

Therapeutic restrictions should be placed on the use of alcoholic beverages which frequently precipitate epileptic seizures. Theoretically it would be best to advise avoidance of any excessive fluid, for overhydration may precipitate convulsions. Finally, the physician should suggest that the patient must avoid, if possible, head injury, and for this reason young men and boys should be advised specifically to avoid participation in football and boxing.

Treatment

Therapy in epilepsy is aimed at control of seizures. This is achieved through a variety of methods which may be used simultaneously or separately and are perhaps best classified as psychologic, medical, dietary and surgical. In addition to these specific methods, it is important to discuss with the patient and his family general measures of control. It is well

also to discuss at the initial interview treatment of the epileptic seizure or convulsion itself. In most instances the patient suffers from too much rather than too little attention during his seizures. It is enough to place the patient in a comfortable unrestricted position during his convulsion so that he may not injure himself. If possible a tongue blade may be inserted between the teeth at the onset of the attack; however, considerable damage can be done by well-meaning observers attempting to force between the clenched teeth an object designed to protect the teeth and tongue. One can advise the patient and his family that although the attack itself is very frightening, only rarely does a patient die during an attack.

General measures—These include the necessity of avoiding excesses and maintaining regular hours of sleeping and eating, for during fatigue and relative hypoglycemia the patient is particularly prone to have epileptic seizures. It is necessary to stress the need for the ordinary hygienic rules of living. The necessity of avoiding unusual emotional stress should be discussed. Relatives must be encouraged to avoid oversolicitous care and protection of the patient.

The social handicap remains out of all proportion to the seriousness of the disease. Much of this social handicap is related to the attitudes of the patient, his relatives and his friends to his illness. The informed physician can do much to modify the attitudes of the patient and his relatives. It is also possible for the physician to make the patient's social adjustment worse by overdosage or improper use of medication.

It is obvious that in certain instances where the difficulty in adaptation is associated with a progressive brain disease, such as Alzheimer's disease or tuberous sclerosis, the physician is as yet helpless in attempting to correct the social maladjustment. In such instances and others it may be necessary for the physician to recommend hospitalization to protect other members of the family.

Psychologic therapy—In any illness in which the social handicap is as great as it is in epilepsy, the frequent need for specific psychotherapy to aid the patient in living with his illness is obvious. In addition specific psychiatric treatment of patients with epilepsy may so alter the stress situation which precipitates attacks as to aid materially in the control of the seizures.

Medical therapy—Medication remains the principal armamentarium[15] of the physician in his treatment of the epileptic patient. However, an occasional patient may find that his infrequent convulsions are less bothersome than daily medication. In such instances there is no need to urge treatment. Phenobarbital, diphenylhydantoin sodium (DILANTIN® sodium) and trimethadione (TRIDIONE®) are the principal drugs used. Medication must be individualized; the proper dosage is one which controls convulsions without any, or with only minimal, symptoms of toxicity. In the use of these drugs certain general rules apply:

1. Begin treatment with a simple and safe drug and minimal dosage.
2. Increase dosage gradually over a matter of weeks until the seizures are controlled or toxic symptoms appear.
3. In most instances use more than one of the drugs simultaneously. The therapeutic action of the drug appears to be synergistic rather than cumulative.
4. Alter dosage gradually and at no time discontinue treatment suddenly.
5. Tailor the medical regimen to fit the patient, for the pattern and timing of his attacks will be peculiar to him.
6. Once the optimal dosage is reached, it must be maintained for years.

Grand mal epilepsy—Infrequent or nocturnal seizures often may be controlled by phenobarbital alone. Administration of this drug may be begun with doses of 0.1 gm. at bedtime. The dosage may be increased gradually to 0.3 or 0.4 gm. in divided doses throughout the day. Initial doses for children are proportional to weight. The most common side effect from phenobarbital is drowsiness, which may disappear with continued use or may be controlled in part by amphetamine sulfate or methylphenidate hydrochloride (RITALIN®). A rash and other toxic symptoms, such as ataxic gait, tremors and blurring of vision, may develop in an occasional patient. All of these

symptoms disappear when the medication is discontinued.

For most patients with grand mal seizures medication is best started with diphenylhydantoin sodium (Dilantin). The initial dose is 0.1 gm. twice or three times a day. It may be increased gradually to 0.6 gm. a day in divided doses. For children less than six years old the initial dose is 0.032 gm. three times a day; for those more than six years old, the initial dose is 0.1 gm. twice a day. The toxic manifestations are seldom serious. They include gastric discomfort and nausea which may be obviated by taking the medicament with meals or with sodium bicarbonate. Hirsutism may be an undesirable side effect in girls and young women. Hyperplasia of the gums is an unpleasant complaint which is said to be retarded by massaging the gums. Frequently the only practical method of control is surgical removal of the hypertrophied gums. More serious symptoms include nystagmus, ataxia and diplopia; these usually respond to reduction of the dose. Fever, polyarthropathy, skin eruptions and blood dyscrasias are encountered rarely from use of Dilantin; when they do occur treatment must be discontinued.

In many patients with grand mal seizures the convulsions are best controlled by the concurrent use of phenobarbital and Dilantin. A satisfactory dosage with which to begin is Dilantin, 0.1 gm. three times a day, with phenobarbital 0.016 gm. three times a day. The dose of phenobarbital may be increased gradually to tolerance beginning with a dose of from 0.032 to 0.1 gm. of phenobarbital at bedtime. An effective dosage for many adults is Dilantin, 0.1 gm., with 0.032 gm. of phenobarbital three or four times a day. These drugs are now available in varying doses in one capsule.

Focal seizures—Treatment of focal seizures is that described for grand mal seizures. In most instances simultaneous use of phenobarbital and Dilantin will be necessary.

Petit mal—Trimethadione (Tridione) is the drug of choice for patients with petit mal. Administration may be begun at 0.3 gm. daily and doses may be gradually increased for adults and adolescents to 2.7 gm. daily in divided doses. Frequently patients complain of hemeralopia and photophobia which may disappear with continued use of the drug. A toxic dermatitis may appear which will respond to withdrawal of the drug. The dosage for children should be proportionate to weight.

Unfortunately the more serious complaints of aplastic anemia, agranulocytosis and nephrosis have been reported from the use of Tridione, and these have necessitated withdrawal of the medication. Because of these complications patients receiving the drug must be observed carefully, and urinalysis and routine blood studies are indicated each month.

Unfortunately Tridione does not control epileptic seizures other than petit mal. For this reason it is best to use it in conjunction with either phenobarbital or Dilantin to protect the patient from grand mal seizures.

Status epilepticus—Status epilepticus is a medical emergency consisting of recurrent seizures; the patient does not recover from one attack before the next begins. Treatment is aimed at control of the seizures and at preserving the life of the patient through maintaining an adequate airway and hydration, and preventing self-injury. Seizures are most readily terminated by the intravenous administration of phenobarbital sodium or amobarbital sodium. Doses of from 0.4 to 0.8 gm. of sodium phenobarbital or from 0.5 to 1 gm. of amobarbital sodium in distilled water are given intravenously to adults. For children approximately half this dose is required. Dilantin sodium and paraldehyde also may be given intravenously, or one of the volatile anesthetics, such as chloroform or ether, may be given by mask for the control of status epilepticus. After control of the status epilepticus maintenance of adequate anticonvulsants is necessary. It is perhaps worth noting that any sudden withholding of medication, such as is sometimes done when making electroencephalograms, may precipitate status epilepticus.

Additional drugs—The bromides, the original anticonvulsant drugs, remain satisfactory, although at present they are seldom used. Numerous additional drugs have been reported as efficacious for epilepsy in recent years. None of these have proved as satisfactory or safe as

phenobarbital, Dilantin and Tridione. When these three drugs have proved ineffective, one may consider the use of one of the newer drugs, recognizing that the toxicity of these drugs is not as yet well delineated. Included among these drugs are mephobarbital (MEBARAL®) and metharbital (GEMONIL®) which are related to phenobarbital and have similar properties. Primidone (MYSOLINE®) is also a barbituric acid analogue and may be used with other anticonvulsants such as Dilantin.

Methoin (MESANTOIN®) and ethotoin (PEGANONE®) are similar in action to Dilantin. Mesantoin appears to be more toxic and Peganone less effective than Dilantin. Phensuximide (MILONTIN®) and methsuximide (CELONTIN®) are reported to be effective for the control of petit mal. Celontin[16] appears to be particularly useful for the patients who have myoclonus during their epileptic attacks. Paramethadione (PARADIONE®) is similar to Tridione in its indications and toxicity. Phenacemide (PHENURONE®) which is reportedly specific for focal seizures (psychomotor seizures) has proved in our experience too toxic for routine use. Acetazolamide (DIAMOX®) in our experience has proved a useful drug in an occasional patient when used as a supplement to routine medication.

Discontinuing drug therapy—When to discontinue medication is a difficult question. Prior to withdrawal of medication the patient should understand and be willing to assume the responsibility for an increased risk of convulsions. If the patient still wishes to consider withdrawal, he should be advised to do it slowly over several months. In addition, it would seem wise for the patient not to discontinue treatment during adolescence or any other period of undue stress.

Dietary therapy—In the past a ketogenic diet has proved successful in the treatment of convulsive disorders.[17] The use of drugs is usually simpler than maintaining a patient on such an unpalatable diet for any length of time. The ketogenic diet now is mainly useful for children whose attacks cannot be adequately controlled with drugs.

Surgical therapy—Surgical treatment has been advocated as the treatment of choice in certain patients with focal seizures. In those patients who are handicapped by focal seizures which cannot be controlled medically, surgical extirpation of the cerebral focus from which the seizures arise may be considered. This form of therapy is still in the process of final evaluation.[2]

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Although antibiotics have produced far more benefits than side effects, the physician should be constantly aware of the indications for and the failures of antibiotic therapy. The author emphasizes the necessity of making an etiologic diagnosis before selecting an antibiotic. He states that multiple therapeutic agents may be indicated in mixed infections and that antibiotics are valuable in prophylaxis. He also points out that new antibiotics have become available for management of staphylococcal infections.

Antibiotic Therapy in Pediatrics

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THE introduction of chemotherapeutic and antibiotic agents has revolutionized the entire field of medicine, including pediatrics. Developments occur at such a rapid pace that it is almost impossible for the practicing physician, the scientist or even the full-time investigator to keep abreast of them. To begin this discussion, I would like to mention some of the newer antibiotics and derivatives of the older ones which are used in pediatrics today.

ERWIN NETER

New and Old Antibiotics

Three of the new antibiotic compounds, kanamycin sulfate, ristocetin (SPONTIN®) and vancomycin, which are currently being investigated have become available primarily for the treatment of staphylococcal infections. These agents must be administered either intravenously or intramuscularly; hence, their use is restricted to patients with severe infections, and particularly hospitalized patients. Kanamycin sulfate also appears to be effective in treating infections caused by Friedländer's bacillus. Patients should be carefully observed for side effects during administration of any of these antibiotics.

Another of the promising antibiotics is amphotericin B (FUNGIZONE®), which has proved effective in treatment of fungous infections, particularly systemic fungous infections. This drug supplements the action of MYCOSTATIN®. The latter is highly effective in treating moniliasis and other localized fungous infections, but it is not beneficial in the systemic treatment of mycoses.

FURADANTIN® has been found useful in treating urinary infection, while another compound of this series, FUROXONE®, has proved promising for treating bacterial enteric infections. Furoxone is administered orally and should be given in divided doses of 5 to 6 mg. per kilogram of body weight over a 24 hour period.

Among the presently used derivatives of older antibiotics are preparations from tetracycline and from erythromycin. Adding phos-

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phate, citrate or glucosamine to orally administered tetracycline enhances to some degree the absorption and hence the blood levels obtained. These compounds show the same efficacy as tetracycline itself, and critical analysis of the data reveals that although these derivatives are valuable they are not strikingly superior to tetracycline alone. If they were, lower doses probably would be recommended. Thus, it is perfectly all right to use them, but one should not expect these derivatives to produce miracles that are not obtained with tetracycline itself.

I would like to re-emphasize the importance of three antibiotics which have been at our disposal for some time, namely, bacitracin, neomycin and polymyxin B sulfate. These antibiotics provide bactericidal action against susceptible organisms, and they are well tolerated when given locally. Bacteria do not readily develop resistance to these antibiotics, and allergic reactions are most infrequent. Therefore, these agents may be used for localized infections more often than they have been in the past. In regard to the local tolerance of these drugs, it is important to remember that intraperitoneal administration of neomycin (for example, in patients with ruptured appendixes) may produce respiratory arrest; thus, this drug should not be given by this method.

I would like to emphasize that even in this age of antibiotics the sulfonamides are still valuable therapeutic agents in pediatrics. Sulfadiazine, sulfamerazine, GANTRISIN®, the triple sulfonamides and the newer, somewhat longer-lasting sulfonamide preparations all appear to be equally effective. These agents are especially valuable in treating acute urinary tract infections; in fact, they are considered the drugs of choice in our hospital. It should be emphasized, however, that a chronic or recurrent urinary tract infection in children probably is due to some anatomic or physiologic obstruction; therefore, it is necessary that the physician explore the pathologic findings of the condition and take the indicated corrective measures. No antibiotic or sulfonamide can eradicate an infection under these circumstances.

The sulfonamides also have produced excellent results in treatment of meningococcal infections, as evidenced by the fact that the mortality from these diseases has been reduced to a phenomenally low figure. Acute bacterial respiratory infections also respond well to sulfonamide preparations, and excellent results have been obtained from use of the sulfonamides in infections caused by *Shigella* organisms. One should remember, however, that penicillin is superior to the sulfonamides in hemolytic streptococcal disease.

Selecting an Antibiotic

In general, the use of antibiotics has produced far more benefits than side effects; however, we should constantly be aware of the indications for and the failures of antibiotic therapy. It has been clearly established that none of the available antibiotics have any effect in viral diseases, with the exception of lymphogranuloma venereum and psittacosis, which are really not viral infections at all. Asian influenza, influenza virus infection, poliomyelitis and infectious hepatitis are not affected by currently used antibiotics.

Since we know that there is no truly broad-spectrum antibiotic that is effective against all disease-producing bacteria, an etiologic diagnosis should be made before an antibiotic is selected. When it has been established that the disease is, perhaps, lobar pneumonia, streptococcal sore throat or the *Bacillus influenzae* infection commonly found in children, an appropriate antibiotic may be selected. It is sometimes necessary to rely on laboratory tests for information as to which of the many bacteria is responsible for the disease in a particular patient.

It would be much easier to recognize the indications for treatment and to select the proper antibiotic for treating the wide variety of infections if we could accurately predict what course the disease would take in the absence of treatment and whether an antibiotic will produce an undesirable side effect in a given patient. Since we often cannot do this, we must rely on statistics. However, we cannot always predict whether a patient belongs in a group classified by statistical studies. I

think this may be illustrated by the story of the physician who recommended surgery for one of his patients. The patient hesitated and then said, "Doctor, tell me first how many patients die during this type of operation?" The doctor replied, "To be frank, 10 of 100 die, but you don't need to worry; my 10 are dead already." We simply do not know whether a given patient is one of the 10 or the 90.

An etiologic diagnosis often can be made on clinical grounds. The presence of scarlet fever rash indicates a streptococcal infection. In serious infections, such as meningitis, it is necessary to have the laboratory determine whether the infection is caused by *B. influenzae, Pneumococcus* or *Streptococcus*. With information from the laboratory tests, the proper drug can be chosen, for example, a sulfonamide for epidemic meningitis, penicillin for pneumococcal or streptococcal meningitis, and chloramphenicol for meningitis caused by *B. influenzae*.

When the antibiotic sensitivity of an organism is not known, in vitro sensitivity tests should be done; however, such tests are unnecessary for the so-called predictable bacteria, such as the *Pneumococcus*, hemolytic *Streptococcus, Meningococcus*, etc. These organisms almost invariably are sensitive to some antibacterial agent.

On the other hand, about 40 to 60 per cent of all staphylococci which cause disease in humans are resistant to penicillin. Many types of staphylococci are resistant to tetracycline, and an increasing number are becoming resistant to erythromycin. Therefore, in treating a seriously ill patient or one whose disease may become worse in a short time, sensitivity testing should be undertaken immediately.

Multiple Therapeutic Agents

Multiple antibiotic therapy may be indicated in mixed infection when a single antibiotic is not effective against the two or three organisms responsible for the disease. Multiple therapy also may be indicated prior to the establishment of the precise cause of the disease; for example, more than one antibiotic may be given in acute meningitis before it is known whether the disease is caused by *B. influenzae, Pneumococcus* or *Streptococcus*. Multiple antibiotics also may be used in order to produce synergism, which is obtained when two drugs act together to yield results superior to those of either drug used alone. For example, in subacute bacterial endocarditis, penicillin used with small amounts of streptomycin gives results superior to those obtained with penicillin alone. Toxicity may be reduced by using only half the amount of an antibiotic which produces side effects and supplementing the dosage with a second antibiotic.

Antagonism between two antibiotics need not be considered a serious problem, despite the fact that interference of one antibiotic with another has been clearly demonstrated in experimental animals. However, multiple antibiotics should not be used indiscriminately.

The adjunct use of gamma globulin in serious infections may be beneficial. Work with experimental animals has shown clear-cut evidence that gamma globulin may be effective against certain bacterial diseases. Even when there is no gamma globulin deficiency in the form of agammaglobulinemia, clinical observation suggests that the adjunct use of gamma globulin may give impressive clinical results in seriously ill patients. However, I must emphasize that gamma globulin should not be administered to every patient with an infection. It is an expensive preparation and not easily obtained; thus it must be used judiciously.

Antibiotics in Prophylaxis

Antibiotics also have been proved effective in prophylaxis. It has been clearly established, for example, that penicillin should be given to all children who have had acute rheumatic fever. Second and third attacks of rheumatic fever occur frequently. In fact, without prophylaxis, about 50 per cent of children have a second attack within a year of the first, and every second, third and fourth attack may shorten the life expectancy. Rheumatic fever almost always is introduced by an acute streptococcal infection, and, since penicillin can prevent streptococcal infection, it is capable of preventing recurrent attacks of rheumatic fever. In our hospital, all patients with rheumatic fever receive 250,000 units of orally

administered penicillin twice a day every day of the year. Alternatively, a long-lasting penicillin preparation may be injected once a month. This regimen has indeed prevented many recurrent attacks of rheumatic fever, although a few breakthroughs have occurred.

Syphilis of the newborn also may be prevented by treating the syphilitic mother with antibiotics during pregnancy.

The physician also should remember that subsequent serious disease may be prevented by effective treatment of a primary infection. For example, successful treatment of otitis media prevents mastoiditis. (I am sure that no otologic surgeon could make a living today by performing operations for bacterial mastoiditis.) We know, too, that treatment of bacterial pneumonia prevents empyema, and there is no question but that empyema has become a much less common disease.

Side Effects of Antibiotics

The story of antibiotics is not just one of triumph. Unfortunately, these agents do produce side effects. With the exception of penicillin, which is an extraordinarily nontoxic drug, all other antibiotics cause some toxicity. For this reason, dosage must be carefully adjusted. I would like to point out that if the normally calculated dose for infection were to be administered to a child who had renal failure, toxicity might result. Practically all antibiotics are excreted by the kidneys, and if this excretion is impaired, the blood level may rise above the tolerated amount. Allergic reactions also are encountered, and more are seen with certain antibiotics than with others. Penicillin seems to cause more allergic reactions than do other antibiotics; however, these reactions are far less frequent in children than in adults.

It is also important to remember that superinfections may develop with the administration of antibiotics. Although an antibiotic may effectively eliminate the bacteria which cause a given infection, it also may act on the normal flora, the bacteria that all of us carry on our mucous membranes and skin. We now realize that physiologically present bacteria are helpful, and an alteration of this flora (for example, in the intestines) may make it possible for a few potentially dangerous bacteria to take over the field after the harmless ones have been eliminated. As a result, secondary moniliasis, staphylococcal infections or infections due to gram-negative bacilli may develop.

The secondary staphylococcal infections, particularly antibiotic-conditioned staphylococcal enteritis, are of particular interest. This type of infection frequently runs a fulminant course and too often results in death. When this infection occurs, an immediate diagnosis should be attempted by microscopic and cultural examination of the feces. If microscopic examination within a few minutes shows that many gram-positive cocci are present, staphylococcal enteritis is suspected. Under these conditions, the antibiotic which gave rise to the development of this secondary condition should be discontinued if at all possible, and an antibiotic effective against staphylococci, such as erythromycin or bacitracin, should be given. In serious cases, kanamycin sulfate or one of the other previously mentioned antistaphylococcal agents may be administered.

Management of Staphylococcal Infections

The problem of staphylococcal infections has become much more serious in the last few years. Particularly difficult to manage are the outbreaks of hospital-acquired staphylococcal infections occurring in nurseries, among surgical patients, and even among medical patients. Some of the nursery outbreaks have resulted in secondary infections in homes. Babies who have acquired the infection in the hospital nursery have been known to transmit it to siblings, parents and other persons. Mastitis may develop in the mother from a staphylococcal infection acquired from the baby.

Postoperative infections must be kept to a minimum. In one instance, an outbreak of infection among surgical patients was traced to an open staphylococcal lesion on the surgeon's forearm.

To control outbreaks of staphylococcal infection, we must first secure accurate information on the incidence of a hospital-acquired infection, particularly insofar as newborn in-

fants are concerned. Since babies often are discharged on the third, fourth or fifth day and since nursery-acquired staphylococcal infection may not become clinically manifest until the sixth, eighth or tenth day or even the third week, it is most important that the physician notify the nursery if infection develops. If each of 10 physicians treating 10 different babies in whom staphylococcal infection developed were to think his was the only case and, therefore, did not report it, the hospital personnel would have no knowledge that the nursery was a breeding ground of a staphylococcal epidemic.

It also should be emphasized that the umbrella of antibiotics is no substitute for the practice of aseptic technics. Housekeeping methods must be thoroughly inspected. We must throw away the dry broom that spreads staphylococci instead of collecting the dirt. We also must keep a close watch for open staphylococcal infection among nurses, physicians and any other persons who have contact with patients in hospitals.

Comment

It is wise to reserve one effective antibiotic for treatment of serious infections. The three previously mentioned agents readily lend themselves for this purpose. In addition, we always must remember that unless antibiotics are indicated, they should not be used. They certainly should not be employed in every appendectomy or herniotomy.

We also must educate the public so that the physician will not receive undue pressure to treat every disease, no matter what it is, with antibiotics. After all, aspirin is still a pretty good drug. On the other hand, we must not alarm the public about antibiotic-conditioned infections. Fear of antibiotics could overshadow the good that they accomplish, and the progress in antibiotic therapy of bacterial diseases is indeed impressive.

MEETINGS *and Postgraduate Courses*

AMERICAN COLLEGE OF CHEST PHYSICIANS, ATLANTIC CITY: Twenty-fifth annual meeting, June 3-7, at the Ambassador Hotel. For further information, write to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11.

INTERNATIONAL MEDICAL CONFERENCE ON MENTAL RETARDATION, PORTLAND, MAINE: July 27-31, at the Eastland Hotel. For further information, write to: Dr. Ella Langer, Department of Health and Welfare, State House, Augusta, Me.

INTERNATIONAL SOCIETY OF INTERNAL MEDICINE, BASEL, SWITZERLAND: Sixth international congress to be held August 24-27, 1960, in conjunction with the Swiss Society for Internal Medicine. For further information, write to: Secretariat of the Sixth International Congress for Internal Medicine, 13 Steinentorstrasse, Basel, Switzerland.

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES, OAK RIDGE, TENNESSEE: Instructional seminars and training courses for 1959:

Pathology, May 11-15
Preclinical I, June 1-5
Thyroid measurements, July 6-8
Thyroid clinical, July 9-10
Preclinical II, August 3-7
Pathology, September 14-18
Preclinical I, October 5-9
Hematology, November 9-13
Preclinical II, December 7-11

For further information, write to: William D. Jones, Medical Division, Oak Ridge Institute of Nuclear Studies, Post Office Box 117, Oak Ridge.

THE AMERICAN INSTITUTE OF DENTAL MEDICINE, PALM SPRINGS, CALIFORNIA: Annual meeting, November 8-12. After July 1, 1959, the Institute will be known as The American Institute of Oral Biology. For further information, write to: Hermann Becks, Chairman, Board of Directors, The American Institute of Dental Medicine, 2240 Channing Way, Berkeley 4.

UNIVERSITY OF OKLAHOMA MEDICAL CENTER, OKLAHOMA CITY: Surgery, radiology and pathology symposium on diagnosis and treatment of thyroid diseases, May 8-9. For further information, write to: Office of Postgraduate Education, University of Oklahoma Medical Center, 801 Northeast 13th Street, Oklahoma City 4.

UNIVERSITY OF PENNSYLVANIA GRADUATE SCHOOL OF MEDICINE, PHILADELPHIA: Postgraduate courses for 1959, presented in cooperation with the Children's Hospital of Philadelphia:

Pediatric advances, May 25-29
Practical pediatric hematology, June 1-5

For further information, write to: Dr. I. J. Wolman, Director of Postgraduate Education, Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia.

Ovarian failure is the fundamental factor responsible for cessation of menstruation at the menopause. Uterine bleeding usually diminishes gradually over a period of several months. Irregular or increased bleeding may indicate cancer of the cervix or endometrium and should be investigated immediately. Most women have only minor symptoms of emotional origin, which may be controlled by psychotherapy. True climacteric symptoms, such as hot flushes, may be managed with ataraxic drugs or hormones.

The Management of the Menopause

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As the menarche, or beginning of menstruation, is the most striking physical phenomenon of puberty, the menopause, or cessation of bleeding, is the most obvious sign of the climacteric or transitional period between active childbearing and senescence. There are many superstitions and much misinformation concerning the menopause and, as a result, most women are apprehensive and fearful as this phase of their lives approaches.

Physiology of the Menopause

Normal menstruation—Menstruation is the periodic discharge of blood and disintegrating endometrium which has been prepared by the action of estrogen and progesterone to receive the fertilized ovum. If conception does not occur, the spiral arterioles of the endometrium become constricted and slough, the endometrium degenerates and is cast off, and another cycle is initiated. Normal menstruation is a result of the anatomic and functional integrity of at least three organs: the anterior pituitary, the ovary, and the endometrial lining of the uterus. The anterior pituitary secretes gonadotropic hormones (follicle-stimulating, luteinizing and luteotropic) which act directly on the ovary, stimulating its production of estrogen and progesterone; these, in turn, act on the endometrium to cause the cyclic alterations of the normal menstrual cycle.

During the early part of each cycle an ovarian follicle and its ovum grow and mature under the stimulus of the pituitary follicle-stimulating hormone. The granulosa cells surrounding the follicle secrete estrogen which acts directly on the spiral arterioles of the endometrium as well as on the glands and stroma, causing them to proliferate. At about the midpoint of the normal cycle, follicle rupture and ovulation occur, and the corpus lute-

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um is formed from the granulosa cells by the action of the pituitary luteinizing hormone. The corpus luteum secretes progesterone, which induces the secretory or progestational change in the endometrium, preparing it for implantation of the fertilized ovum. If fertilization does not occur, the activity of the corpus luteum is maintained until about the twenty-third or twenty-fourth day of the cycle, after which its function diminishes rapidly. This, in turn, eliminates the growth stimulus to the endometrial structures. As a result, the arterioles become constricted and lose their integrity, permitting blood to seep into the endometrial stroma, and the endometrium sloughs and is cast off as the menstrual discharge. A normal menstrual period occurs, therefore, as a result of the temporary withdrawal of ovarian hormone stimulation. If conception does occur, the activity of the corpus luteum continues and the endometrium, rather than sloughing, grows and is transformed into decidua.

Abnormal bleeding—Abnormal uterine bleeding can occur as a result of tissue destruction by tumors, injury or infection, or because of abnormal and irregular hormonal stimulation of the endometrium. When the orderly events of the menstrual cycle are disturbed by alterations in the production of pituitary hormones or in the response of the ovary, the endometrium is stimulated irregularly and as a consequence irregular bleeding occurs. As a general rule, a fall in ovarian hormone level below that necessary to maintain endometrial growth permits the endometrium to disintegrate and bleed. This is true of both normal menstruation and bleeding caused by disturbance in hormone production.

Menopause—The menopause usually occurs between the ages of 47 and 50. Some women stop menstruating earlier, occasionally even during the latter part of the fourth decade, while others may continue to bleed regularly until the age of 55. It has been said that the periods will continue longer in women who begin to menstruate while very young than in those in whom the menarche is delayed, but this is not necessarily true.

The fundamental factor responsible for complete cessation of menstruation at the menopause is ovarian failure. During the climacteric period the ovary gradually loses its ability to produce first progesterone and later estrogen in response to the stimulus of the gonadotropic hormones. Pituitary function, as evidenced by high levels of serum and urinary gonadotropins, continues for some time after menstruation ceases. The first function to fail is that of ovulation and corpus luteum formation; estrogen is produced irregularly and in diminishing amounts; finally, bleeding ceases when the estrogen level becomes too low to stimulate growth of the endometrium. Irregular bleeding during the climacteric occurs because the ovary responds irregularly to pituitary hormone stimulation; as a consequence, estrogen production rises and falls at unpredictable intervals instead of rhythmically as it does with normal menstruation.

Uterine bleeding during the climacteric should decrease because ovarian hormone levels are diminishing. In some women the amount and duration of flow gradually become less while the cycle remains fairly regular; these women may either stop bleeding suddenly or miss periods from time to time, eventually stopping completely. In others the interval between periods of bleeding lengthens gradually as the flow diminishes; these women bleed irregularly but less and less. In a few women the periods remain regular in timing and in volume until they suddenly cease.

Although an increase in bleeding can occur if estrogen production is irregular and abnormal, a decrease in length of the cycle, prolonged and heavy periods, and intermenstrual spotting and bleeding are not characteristic of the climacteric and should be cause for concern. Bleeding of this type may be caused by cervical or endometrial cancer, which appears relatively frequently in women of climacteric age.

Menopausal Changes

The changes which occur during the climacteric period and after the menopause are caused by withdrawal of the growth stimulus of the ovarian hormones; therefore they affect the reproductive organs primarily. The vaginal mucosa loses its rugose appearance and be-

comes smooth and pale. Since proliferation of the epithelium is no longer stimulated by ovarian estrogen, it is thinner and is made up only of a few layers of basal cells instead of many layers of cornified cells as it is during active reproductive life. This can be demonstrated in vaginal smears. The uterus becomes smaller and smaller and eventually may regress to a size comparable to that in a young child. The endometrium also is thin and inactive. All these regressive changes can be reversed by the administration of estrogenic substances.

Menopausal Symptoms

Many symptoms are attributed to the menopause but few are actually caused by ovarian failure. Some of the distressing sensations which climacteric women experience are undoubtedly of emotional origin and are related to the disturbing psychic effect of having reached the end of their reproductive lives and of entering the senescent phase. A minority of women experience symptoms of any great severity. The degree of disability is usually determined by the basic personality of the patient, how secure she is as an individual, and various environmental factors. Many women are conditioned to expect annoying or even disabling symptoms by their mothers or misinformed friends.

Vasomotor symptoms—The most common and probably the basic subjective symptom of the climacteric period is the hot flush. This is a specific sensation described as a sudden feeling of intense heat and flushing of the skin of the face and upper part of the body, often followed by profuse perspiration and chilliness. Flushes may occur only occasionally or many times each day and are particularly distressing when they recur repeatedly during the night.

The cause of hot flushes is not definitely known. If they were the result of estrogen deficiency alone, one might expect them to occur in prepuberal girls and in women with amenorrhea secondary to pituitary failure, but they are not experienced under these circumstances. They may be related to the high levels of pituitary gonadotropic hormones, but this has not as yet been definitely established.

Nervous symptoms—Some of the secondary symptoms of the climacteric, such as insomnia, vertigo, fatigue, headache and depressions, are basically of emotional origin and cannot be considered as due solely to the menopause. It is easy to understand, however, why these symptoms appear in women who are afraid of the results of the menopause and are not completely aware of what to expect, particularly if they are experiencing one hot flush after another both day and night.

Insanity, involutional melancholia and similar mental disturbances do occur during the climacteric period, but an emotionally normal woman will not become psychotic because of cessation of menstruation. Serious emotional problems which become manifest at this time develop only in women with an underlying predisposition. The menopause can *precipitate* emotional breaks but not *cause* them.

Many women experience an increase in libido after the periods cease because they need no longer be concerned about pregnancy. In others who are less stable emotionally sexual desire decreases. Sex response and activity need not be altered after the menopause unless atrophic changes in the vagina cause discomfort during coitus.

Diagnosis of the Menopause

Since the menopause occurs as a result of ovarian failure, the diagnosis cannot logically be made in women who continue to bleed regularly; menstruation can only occur if the ovary is functioning reasonably normally. By the same token, women who are bleeding regularly cannot experience menopausal symptoms which occur only because of the great changes in hormone production as ovarian function fails. Many symptoms, such as insomnia, nervousness, headache, fatigue and mental depression, which stem from emotional problems unrelated to function of the reproductive organs are attributed to the menopause by both patients and their physicians simply because they appear at the time of life when the menopause can be expected.

Increased climacteric bleeding of any type cannot be attributed to climacteric disturbances in hormone production unless carcinoma

of the endometrium and cervix is eliminated by adequate biopsy and curettage. Bleeding should decrease during the climacteric and it should cease permanently with the menopause.

An occasional woman may conceive late in her reproductive life; consequently pregnancy as well as the menopause must be considered as a possible cause for the sudden cessation of menstruation.

Treatment of the Menopause

The only women who need active treatment during the climacteric period are those who experience subjective symptoms attributable to the alteration in endocrine function. All women in the menopausal age group, however, should be given a general physical examination, including careful inspection of the cervix as well as a bimanual examination, at least twice a year. Material should be collected from the cervix for cytologic examination once a year and biopsy should be performed on obvious cervical lesions.

Psychotherapy—The periodic health examination provides an excellent opportunity to discuss the menopause with women who are approaching the climacteric phase of their lives. Few of them are aware of the physiologic changes responsible for the cessation of menstruation and many have bizarre ideas as to what to expect. Their fears generally revolve around loss of attractiveness to their husbands, bodily changes such as obesity and excessive hair growth, inability to continue sexual relations, the development of psychoses, and aging. In most instances their children are no longer dependent and women find they have many more free hours in the day than they have ever had and few know how to make use of them. Those who have no hobbies or no interests outside the home are likely to become despondent because they feel they are no longer needed; they can visualize only long, empty years during which they will become older, less useful and less attractive.

Many of the emotional problems which develop during the climacteric period can be prevented or relieved by simple superficial psychotherapy which can be administered by the family physician. A sympathetic discussion of the problems of the climacteric phase of life will often reduce the need for drug therapy or even eliminate it completely. These women need to be reassured that they can remain attractive, that they need not necessarily become old simply because the periods cease, and that they can occupy an important place in society. It often is necessary to direct them toward activities in which they can make a definite contribution.

Women with profound personality changes and severe depression need intensive psychotherapy and should be referred to psychiatrists.

Drug therapy—In the majority of women menopausal symptoms are mild and can be controlled by superficial psychotherapy or by mild sedatives such as phenobarbital, 16 to 32 mg. (¼ to ½ gr.) three or four times daily. This will reduce nervousness and aid in correcting insomnia.

The ataraxic drugs, particularly meprobamate and the *Rauwolfia* compounds, are also helpful in controlling the milder symptoms; 400 mg. of meprobamate three or four times daily is usually sufficient.

Hormone therapy—Endocrine therapy is necessary in a minority of climacteric women. Hormones should never be administered routinely simply because a patient reaches the climacteric phase or because her periods cease. They should be reserved for those who have symptoms which cannot be controlled by simple measures.

Estrogens—The main reason for estrogen therapy in menopausal women is to control hot flushes which recur frequently and interfere with sleep or with the patient's usual activity during the day. One should be reasonably certain that the symptoms actually are associated with estrogen deficiency and are not of emotional origin before prescribing the hormone. Women who are menstruating regularly and those who are bleeding irregularly from hyperplastic endometrium do not have estrogen deficiency.

Estrogen can almost always be administered orally and one has a choice of many effective preparations. It is well to become familiar with the effects of one or two and to use these when treatment is necessary.

Diethylstilbestrol, a synthetic material with estrogenic activity, is inexpensive and will almost always control estrogen-deficiency symptoms. It is administered in doses of 0.5 to 1.0 mg. nightly and within a few days will eliminate the flushes. Most women need substitutional therapy for several months until they adjust to the altered hormone levels, but the adjustment may be delayed if estrogen is administered continuously. The patient can be instructed to take the drug nightly for three weeks, during which time she will be free from symptoms if the dosage is adequate. It may then be discontinued until symptoms recur, when she is instructed to take it again for another three weeks. The symptom-free intervals without therapy will gradually become longer until finally administration of the drug can be discontinued permanently.

Conjugated natural estrogens such as PREMARIN® can be administered in doses of 0.62 to 2.5 mg. daily with equally good results. Although this preparation is somewhat more expensive than stilbestrol, it is a little less likely to cause nausea. One of the most potent estrogenic preparations available is 17-ethinyl estradiol, which is administered in doses of 0.02 to 0.05 mg. These preparations are prescribed intermittently as is stilbestrol.

In an occasional patient who cannot take estrogens by mouth the hormone can be administered by intramuscular injection. Estradiol benzoate, 1.0 mg., can be given twice weekly or estradiol dipropionate once weekly.

If the symptoms are not relieved by estrogen therapy, either they are not a result of estrogen deficiency or the dosage is inadequate. If a vaginal smear shows a full estrogen effect it is unlikely that an increased dose will prove effective. Symptoms can almost always be controlled by an amount less than that required to produce complete cornification of the vaginal mucosa. On the other hand, if the estrogen effect on the vaginal cells is minimal an increase in dosage may alleviate symptoms.

Estrogenic preparations should not be prescribed for women with malignant tumors of the uterus or breasts or those who are bleeding abnormally. They should be used with caution in patients with uterine fibroids.

Androgens—If there is some contraindication to the use of estrogenic substances, hot flushes can be controlled with androgenic steroids. These not only eliminate the distressing vasomotor symptoms, but they also increase sexual desire and produce a general sense of well-being. Unfortunately, however, they often have a masculinizing effect, causing acne, hair growth, and deepening of the voice when used regularly.

The symptoms can usually be controlled with methyltestosterone, 5 to 10 mg. daily, or by administering a combination of androgen and estrogen (10 mg. testosterone and 0.04 mg. ethinyl estradiol).

Summary

The menopause, or complete cessation of menstrual bleeding, occurs as a result of the termination of active ovarian function. Ordinarily uterine bleeding diminishes gradually over a period of several months preceding the menopause. Increased and irregular bleeding may be caused by cancer of the cervix or endometrium and should not be considered to be normal. The majority of women have minor symptoms or none at all during the climacteric period and need no treatment other than reassurance and careful periodic health examinations. True climacteric symptoms can be controlled by judicious use of ataraxic drugs or hormones.

To prove that gout is not a stereotyped disease, the authors report a case in which acute gout simulated an abscess of the thenar space. They suggest that the possibility of gout should be considered in diagnosing any poorly explained inflammatory process in or about a joint, tendon or bursa in a man more than 35 years old. Provocation, onset, site and pain are specific diagnostic points.

Gout Masquerading as Abscess of the Thenar Space

NEWSOM STOOL* AND EINER W. JOHNSON, JR.†

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INITIAL attacks of gout often simulate localized trauma or infection. Patients with gout frequently can recall having had a "sprained ankle" or "infected toe" long before their disease was diagnosed. Seldom, however, does an initial attack assume such a cloak and mask as in the case reported in this discussion, which is presented to alert surgeons to the vagaries of acute gouty inflammation.

NEWSOM STOOL

EINER W. JOHNSON, JR.

Report of Case

A 47 year old white office worker came to the emergency room of the Rochester Methodist Hospital on July 14, 1957. He complained of pain and swelling in his right hand. He stated that approximately 36 hours previously he had awakened in a sitting position while traveling on a commercial airliner. A dull, diffuse pain in the region of the first metacarpus was attributed to the pressure of sleeping on his hand. But pain, followed by swelling, steadily progressed and was moderately intense by the following day. He recalled no trauma to his hand or wrist other than possibly sleeping on the hand. He had experienced no similar episodes in the past.

Physical examination revealed guarding of the position and the movement of the right hand. The patient was moderately obese. Vital signs were normal except for an orally determined temperature of 99.7° F. Marked swelling extended from the thenar eminence to the dorsal aspect of the web of the thumb and index finger. Slight swelling extended into the

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midpalm and the volar aspect of the wrist and lower forearm. Tenderness was diffuse but seemed to center about the base of the thumb, where it was greatest and was accompanied by slight erythema. Findings in the remainder of the physical examination were normal.

The chest roentgenogram and results of routine tests of blood and urine were normal on admission. A roentgenogram of the hand revealed a rounded soft-tissue density measuring 5 by 7.5 cm. in the thenar area (figure 1).

The patient was admitted to the hospital with a diagnosis of abscess of the thenar space. One million units procaine penicillin G and 0.5 gm. streptomycin-dihydrostreptomycin sulfate (DISTRYCIN®) were administered every eight hours. Eighteen hours after admission the inflammatory mass had subsided to a considerable degree.

Nevertheless, an exploration of the area seemed indicated, and the thenar space was approached through a dorsal incision. No pus was encountered. There was moderate soft-tissue edema and scanty serous fluid. No synovium was visualized. Subsequently, results of bacteriologic studies of the fluid proved to be negative.

Because of the presence of nonsuppurative inflammation following an acute, labile course, gout was suspected. A determination of serum uric acid on the day following exploration was 9.6 mg. per 100 ml. A leukocyte count was 6800 cells per cubic millimeter. The patient was examined again, and it was noted that he had experienced symptoms of inflammation of the Achilles tendon one month previously. These symptoms had been attributed to a "bruised calf." No tophi were found. Subsequent follow-up by a consultant in rheumatology confirmed the diagnosis of gout. The operative wound healed uneventfully and all signs of inflammation subsided promptly.

Comment

Of the sources of infection of the thenar space discussed by Bunnell,[1] two anatomic sites are suspect in this case. Either synovitis of the first metacarpophalangeal joint or radial bursitis may be involved, but the former seems more likely. The unique features of this case

FIGURE 1. Right hand, showing soft-tissue density of thenar space.

are (1) the unusual site of an early attack of gout and (2) the extent of exudation in the confined tissue space. No similar case was found in either textbooks or case reports.

Gouty involvement of the upper extremities is uncommon in early attacks. In a study of 100 cases, Hench, Vanzant and Nomland[2] found that initial attacks affected the shoulder in 1 per cent and the wrist in 1 per cent of cases. Involvement of the metacarpophalangeal joint by well-established disease was not unusual; 58 per cent of their group of patients had early involvement of the great toe. Comroe,[3] however, declared the great toe to be involved ultimately in 90 per cent of cases. Most physicians will recognize podagra, but what becomes of the remaining 42 per cent of cases in which symptoms are not present in the classic location? In the study of Hench and co-workers, an average of 10 to 15 years elapsed between the onset of the disease and its recognition. Obviously many minor and occasional major episodes of early gouty inflammation are not diagnosed. One can only speculate on the number of cases treated as nonspecific cellulitis, tendinitis or bursitis which eventually prove to be gout.

It is suggested that effort be made to determine whether or not gout is present in any poorly explained inflammatory process in or

about a joint, tendon or bursa in a man more than 35 years old. The following are specific points of diagnostic value:[4]

1. *Provocation*—Spontaneous attacks of acute gout often occur, but a recent history of trauma, surgical operation or excesses of alcohol or food may be linked to exacerbations.

2. *Onset*—When provocation plays a role, a latent period follows the provocative incident. This may vary from a few hours to a few days. Once it begins, the pain increases rapidly and reaches maximal intensity in from 12 to 36 hours.

3. *Site*—Usually a peripheral joint or its environs are involved, but olecranon bursitis and inflammation of the Achilles tendon are additional common manifestations of acute intermittent gout.

4. *Pain*—Classically, a diagnostic attack is attended by an intense, often pulsating pain. Some attacks, however, may be so mild that medical aid is not sought. Pain which is disproportionate to trauma should arouse suspicion of gout.

An often neglected but helpful therapeutic test is the intravenous use of colchicine,[5] which only recently has become available on the drug market. The average dose is 3 mg. It is an effective and often rapid method of alleviating acute gout, and is especially valuable for preoperative or postoperative patients in whom gastrointestinal side effects should be avoided.

Summary

A case of acute gout simulating abscess of the thenar space is reported. It is pointed out that gout is not a stereotyped disease. Suggestions which may aid in its early recognition are presented.

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Postgraduate Clinical NOTES

114. GOUT

It has been emphasized in the literature that the clinical pattern of gout is easily recognizable, and this emphasis is certainly justified since one sees typical cases misdiagnosed even at present. The criteria for the diagnosis have been well summarized by Cohen, as follows: the disease is characterized by attacks of acute arthritis that, during the early phases, are followed by complete remission of all bone and joint symptomatology; the disease occurs chiefly in males, with its onset principally in the age range 30 to 50 years; a family history of gout is often found; hyperuricemia is usual at some time during the course of the disease if uricosuric medication is not given; acute gouty attacks characteristically follow operative procedures, trauma, strenuous exercise, the discontinuance of steroid therapy, and the administration of certain drugs such as liver, mercury and ergot; tophi, either subcutaneously or in bone, are pathognomonic; a good response of joint symptoms to colchicine is an excellent sign favoring the diagnosis.

Goldthwait et al., Diagnosis of gout, *New England Journal of Medicine*, December 4, 1958, pp. 1095-1099

Teratomas are predominantly tumors of infancy, usually detected during the first two years of life and occurring twice as frequently in male as in female children. Like other tumors of childhood, they often are benign but have serious potentialities of malignancy. The author describes several types of teratomas removed at the Children's Hospital, Louisville. He suggests microscopic diagnosis within 24 to 48 hours after a patient's admission to the hospital, with total excision the only logical procedure.

Teratomas in Children

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ANY tumor which contains the elements of the three germ layers, endoderm, mesoderm and ectoderm, may be considered a teratoma. Tumors of this type contain multiple tissues of types foreign to the part or area in which they are located. They should not be confused with the mixed tumors which develop from anlage within specific organs or areas. The so-called fetus in fetu probably does not justify a separate classification since it is actually a form of teratoma. Most dermoids are, in fact, teratomas.

Teratomas are usually cystic or partially cystic in consistency, although completely solid teratomas do occur. The most constant finding is the variability of tissues. Those most commonly found are sebaceous material, hair, teeth, bone and cartilage, respiratory and alimentary epithelium, and vascular tissue. It is generally reported that a large amount of neural tissue is present in at least 80 per cent of teratomas. This figure approached 100 per cent in the cases of teratoma observed at the Children's Hospital. Many of these structures can be recognized on the cut surface of the gross specimen. The teratoma shown in figure 1a and b contained a large amount of fat, but cysts, bone, cartilage and neural tissue all could be identified when the fat was dissected away. Benign teratomas are usually made up of mature cells. Wildly proliferating immature elements are characteristic of malignancy here as in all tumors.

It should be emphasized that it is often impossible to predict the future growth of this tumor by its histologic appearance; its very nature makes extensive serial sectioning necessary in order to eliminate the probability of missing small areas of malignant tissue. As a rule, benign teratomas are well encapsulated so that the entire tumor can be shelled out without difficulty, and a rather satisfactory prognosis made on the basis of gross examination. The presence of areas of necrosis or hemorrhage is strongly suggestive of a malignant tumor. The modest size of the vessels supplying these tumors has been quite striking in

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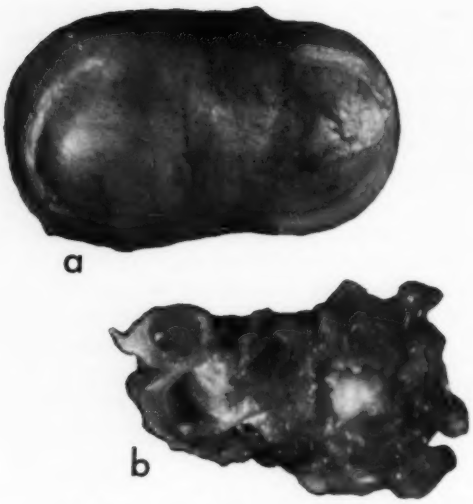


FIGURE 1a. Teratoma containing a large amount of fat; b, cysts, bone, cartilage and neural tissue are visible after removal of the fat.

most instances. In several cases, the vessels actually seemed inadequate to support growth and the operator appeared to be exercising an undue amount of caution in searching for hidden blood supply.

In a period of four and a half years, teratomas of the neck, chest, abdomen, pelvis, sacral region, testes and thoracolumbar portion of the vertebral column have been encountered at the Children's Hospital (figure 2). In two cases, the tumor originated in the testis. In one of these cases, the patient died of metastatic involvement of the pelvis, abdomen, lungs and other portions of the body.

Contrary to the experience of Willis,[1] we have found that the most frequent site of teratomas in children is the sacrococcygeal region, although these tumors may occur almost anywhere in the body. The next most frequent site would appear to be the retroperitoneal region along the paravertebral gutter. According to Willis,[2] teratomas arise in order of frequency (regardless of the age of the patients) in the ovaries, testes, anterior mediastinum, lumbar gutters, presacral and coccygeal regions, within the skull, and in the neck.

Teratomas are predominantly tumors of infancy. Because of their size and location, they usually are detected in the first two years of life, if not at the time of birth. Teratomas of the ovary, testis and mediastinum usually are detected at a later age than those in other areas. One can only speculate as to whether these originate during early development and remain quiescent during infancy and childhood, only to grow actively as malignant tumors in adolescence.

Teratomas are twice as frequent in males as they are in females. This appears to be rather universally true except for the intracranial teratomas, which apparently occur almost exclusively in males. The fact that most of these teratomas appear on the left side is difficult to explain.

Clinically, this tumor presents little in the way of a diagnostic challenge. Except for the sacrococcygeal type, it has been the experience of most clinicians that patients with a teratoma have been appropriately referred to operation with the wrong pathologic diagnosis. Since a teratoma is less frequently encountered in the abdomen than is a neuroblastoma

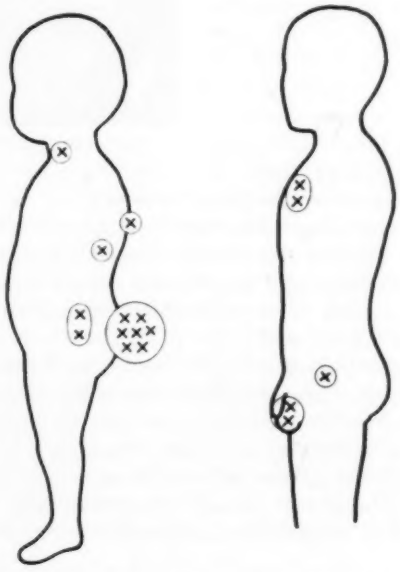
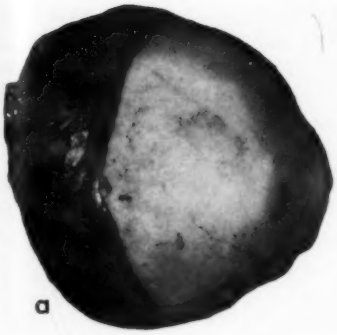


FIGURE 2. Anatomic site of teratomas encountered at the Children's Hospital in a period of four and a half years.



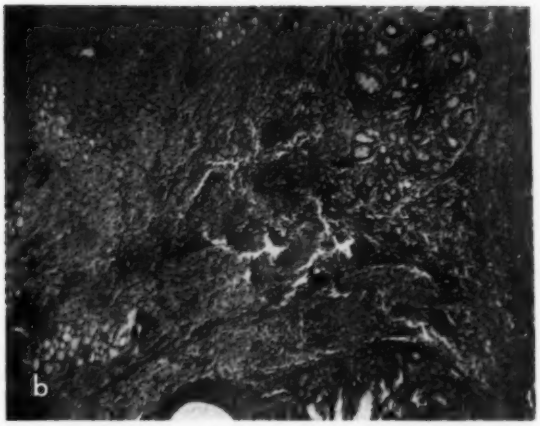
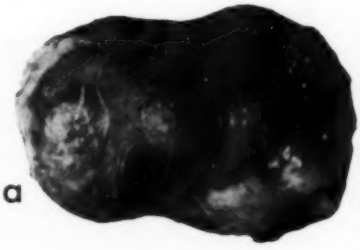


FIGURE 3a. Sacrococcygeal teratoma which weighed 1 lb.; b, section of tumor showing ducts and acini of a salivary gland and intestinal mucosa.



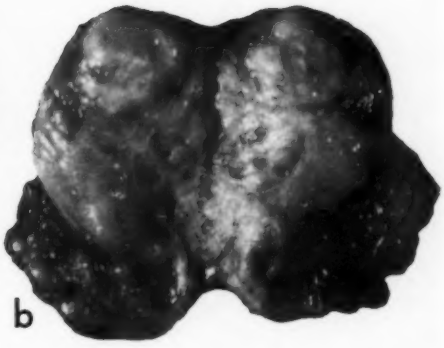


FIGURE 4a. Teratoma removed from the neck; b, cut surface of tumor showing neural tissue.

or the Wilms tumor, it is only natural that these more common growths are usually suspected in this area. Its relative rarity elsewhere in the body also accounts for the frequent failure in diagnosis.

In any case in which a patient is admitted to the Children's Hospital because of the presence of a lump, bump or mass, it is our policy to make a microscopic diagnosis within 24 to 48 hours whenever this is possible. There has never been occasion to regret this policy. The diagnosis of benign tumor relieves the parents' anxiety and eliminates all doubts. The diagnosis of a malignant tumor confirms the parents' worst fears, but offers the possibility of cure and may give long-range consolation. Parents who have failed to note a grapefruit-sized mass in the infant's abdomen are naturally anxious to shift any blame or guilt. Hav-

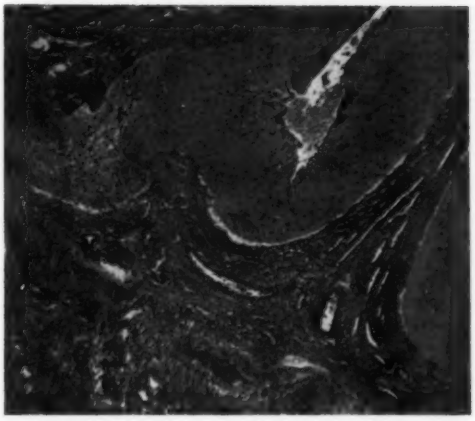


FIGURE 5. Neural tissue and ependyma-lined spaces in section of gross tumor shown in figure 4.

FIGURE 6. Abdominal teratoma removed from an 11 month old girl.

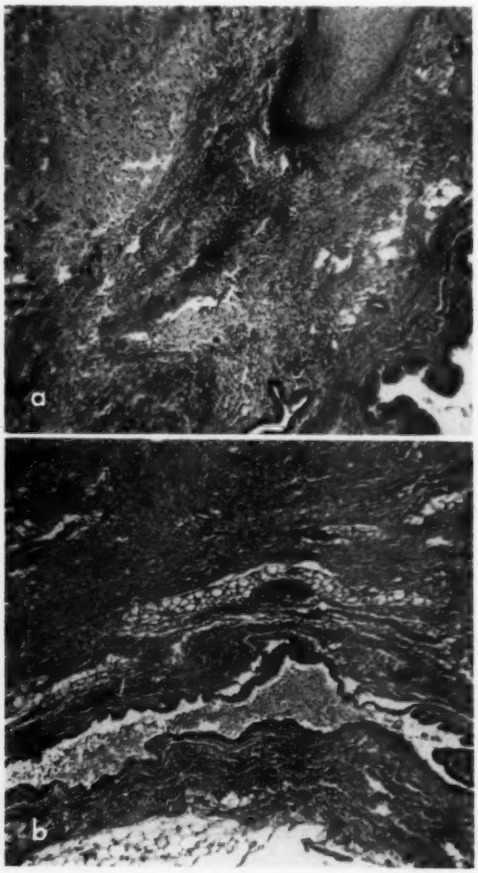


FIGURE 7a and b. Sections of tumor shown in figure 6.

ing the child in the hospital for not more than 24 hours before the operation helps to avoid this tendency. If the parents know that the tumor received immediate attention, it protects the reputation of both the hospital and the doctor.

During the day that the child is in the hospital before the operation, a blood count and an intravenous pyelogram are made, the urine is examined, and the blood is typed and crossmatched. This time also is adequate for any additional diagnostic or therapeutic procedures, such as examination of the bone marrow, roentgenographic examination of the chest, abdomen, long bones and skull, or blood transfusion. Prompt completion of these procedures prepares the patient for excision of the teratoma.

Early removal of a large sacrococcygeal teratoma is indicated. Figure 3a shows the grotesque appearance of a 1 lb. teratoma which was removed from the sacrococcygeal region of a newborn infant who weighed 8 lb. The tumor contained ducts and acini of a salivary gland as well as intestinal mucosa and many other structures (figure 3b). In the removal of this type of teratoma, conservation of the perianal skin is desirable. It has become our practice to remove the coccyx as part of the tumor mass, and to take great pains to protect the posterior wall of the rectum from injury.

Figure 4a shows a teratoma which was removed from the lower and anterior portion of the neck just above the clavicle and the manubrium. This site would seem to be above but comparable to the site of teratomas of the anterior part of the superior mediastinum. On the basis of the appearance of the cut surface of the tumor (figure 4b), one could be almost confident that neural tissue was present. The presence of such tissue was confirmed by microscopic examination, which disclosed neural tissue and ependyma-lined spaces (figure 5).

Almost 100 years ago, the theory was advanced that these tumors of the neck and mediastinum arose from abnormal development of the third and fourth branchial clefts. This would certainly explain their anterior location in the mediastinum, their adherence

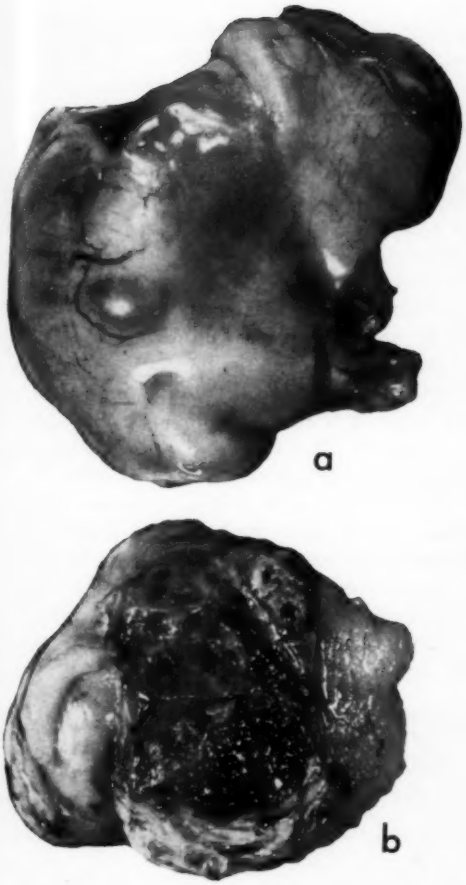


FIGURE 8a. Malignant teratoma removed from left side of the scrotum; b, cut surface of tumor showing hemorrhagic, necrotic and cystic areas.

to great vessels and pericardium, as well as their location in the anterior part of the neck. We recently have observed a case of asymptomatic teratoma of the lower part of the anterior mediastinum in which the weight of the enlarging tumor appeared to be responsible for its inferior location. Entrance of the blood supply from the superior aspect of the tumor indicated it had originated at a higher level.

Figure 6 shows the cut surface of a teratoma which was removed from the abdomen of an 11 month old infant. Cartilage, neural tissue and fat can easily be identified. The presence of these tissues was confirmed by microscopic

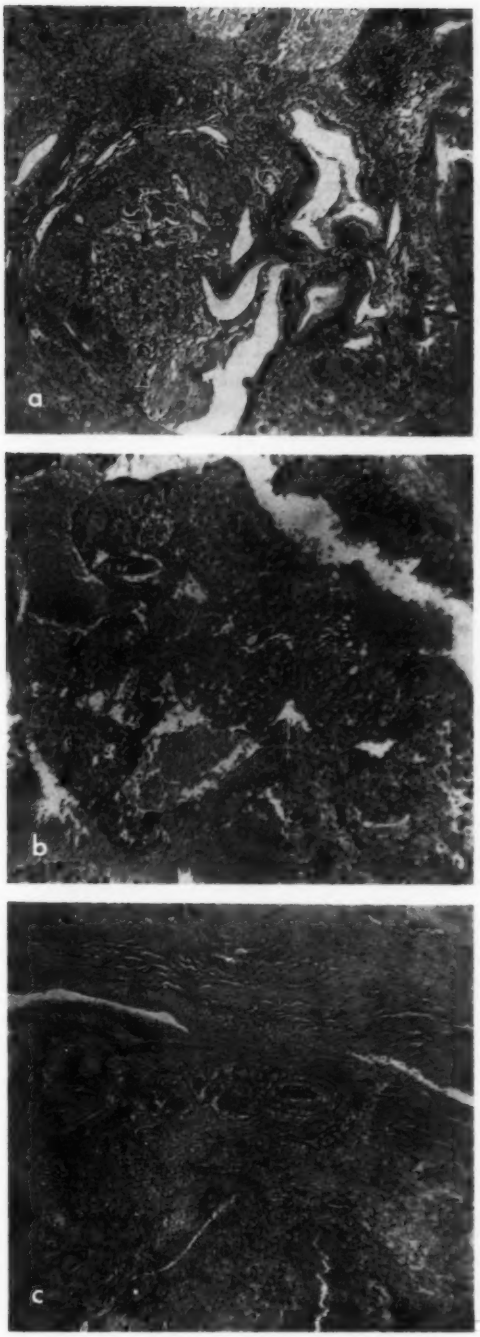


FIGURE 9a, b and c. Sections of gross tumor shown in figure 8a and b.

examination (figure 7a and b). The blood supply of the tumor was derived from the vessels of the left kidney. The tumor was easily removed, but in ligating the vessels the renal blood flow was partially impaired. Within four weeks after the operation, marked hypertension and enlargement of the heart developed. The infant was readmitted to the hospital because of congestive heart-failure. The left kidney was removed. The heart and blood pressure returned to normal very rapidly after this operation. The infant has been free of symptoms for the past year and a half.

As previously mentioned, we have observed two cases of malignant teratoma of the testis. Figure 8a shows the gross tumor which was removed from the left side of the scrotum in one of these cases. The patient, who was a young man, said that a lump had been present in the left side of his scrotum for at least seven years. His symptoms were due to rapid growth of the tumor and to metastasis. The cut surface of the tumor (figure 8b) reveals small hemorrhagic, necrotic and cystic areas, and shows that the normal testis had been pushed well to the periphery. Figure 9a reveals a bizarre picture. There are epithelium-lined spaces, and malignant chorionic cells with dark cytoplasm are intermingled with malignant seminoma cells with light cytoplasm. Figure 9b shows the presence of multiple vacuoles, which were thought to be indicative of a high degree of malignancy. Figure 9c reveals seminoma cells which are making an abortive attempt to form seminiferous tubules.

In any discussion of teratomas, it is only fitting to quote G. W. deP. Nicholson, late professor of pathology at Guy's Hospital in London. This author[3] said, "There are two ways of regarding a teratoma: as an aborted organism that has failed, to use a popular figure of speech, to produce an orderly soma, or as a malformation that has partly succeeded, creditably on the whole, in producing a number of somatic tissues. In the former view the teratoma is analogous to the double monsters, in the latter it is relegated to the hamartomata or tumours. The thing we see remains the same; it is our interpretations that differ."

Teratomas as well as other tumors of childhood, though often benign, have serious malignant potentialities. Total excision of every undiagnosed mass as soon as possible after its detection is the only sane and logical procedure so far as the patient, the family and the doctor are concerned.

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Infections of the urinary tract result from bacterial invasion. Diagnosis is made by urinalysis. In the presence of a second acute attack or persistent infection, further diagnostic procedures should be carried out. The sulfonamides are probably the drugs of choice for acute infections. Although the newer antibiotics and chemotherapeutic agents are highly effective in acute uncomplicated infections, they are less successful in chronic and recurrent infections. Antibiotics should not be used routinely.

Infections of the Urinary Tract

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INFECTIONS of the urinary tract occur frequently and in all age groups. They result from bacterial invasion, and may cause no apparent symptoms or such serious symptoms as dysuria, frequency, flank pain, fever and chills. Dysuria, frequency and urgency, which are referable to the lower urinary tract, are more common in pyelonephritis than are flank pain, chills and fever. Although cystitis may occur without renal involvement, there is no reliable way to distinguish pure cystitis from cystitis with renal involvement. It is advisable, therefore, to treat all patients with urinary tract infection as though infection of the kidneys were also present.[1]

Modern antibacterial therapy has not noticeably affected the incidence of pyelonephritis. Several observers have found pyelonephritis in from 12 to 20 per cent of all cases studied at autopsy, while the diagnosis during life was made in only one-fifth of the patients. This large discrepancy between clinical and autopsy findings can only be explained by the fact that there were no urinary symptoms.

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Diagnosis

The diagnosis of urinary tract infection is made by urinalysis. The urine should be obtained from female patients by catheterization, while male patients should provide a clean, voided midstream specimen. If infection is present, the fresh urine should show five or more leukocytes per high-power microscopic field, and 100,000 or more organisms per milliliter of urine when a culture is prepared. Only freshly voided urine or a sample obtained by catheterization should be examined; if the specimen stands, the bacteria multiply rapidly and the pus cells disintegrate, so that results of any such study have no significance.

Garrod, Shooter and Curwen[2] have presented a good clinical classification of infections

of the urinary tract. They divided their patients with urinary infection into three groups: (1) patients without abnormalities of the urinary tract and without a history of previous urinary infection. Prognosis in this group is good; about 90 per cent of the patients can be cured, as judged by the disappearance of symptoms and elimination of leukocytes and bacteria from the urine; (2) patients with a previous history of urinary infection. The prognosis is only moderately good in this group, with only 60 per cent of the patients cured when re-examined two to four months after the initial infection; (3) patients with definite abnormalities or obstructions. The prognosis is poor; only 26 per cent of their patients were cured unless the obstruction was eliminated.

Of the patients who did not respond completely to treatment, 46 per cent showed superinfections; that is, the original bacteria had disappeared but other organisms were present on the subsequent cultures. These superinfecting organisms are, as a rule, resistant to antibiotic therapy. Normally, in man, there is a happy balance in the bacterial flora so that invading organisms and the host organisms lead a symbiotic existence. Antibiotics can disturb this balance to pathologic proportions, suppressing the common gram-negative and gram-positive organisms, and allowing the others to multiply actively. The resistant organisms, such as *Pseudomonas*, *Proteus*, *Aerobacter aerogenes* and *Candida*, grow and cause serious superinfections which are difficult to treat.

The organisms commonly found in infections of the urinary tract are *Escherichia coli* and closely related bacteria. The organisms mentioned in the preceding paragraph appear in chronic and complicated infections, and particularly following instrumentation or previous antibacterial treatment. The urine culture and sensitivity tests are important, since large series of cases show a high correlation between the in vitro and in vivo results. Nevertheless, microscopic examination of fresh urine and a Gram test of the sediment can give useful clinical information as to whether there is a high bacterial count, the type of organism present, and the type of treatment indicated.

If there have been two attacks of acute urinary tract infection or persistent infection, certain studies should be made. These include urine culture and sensitivity tests, followed by intravenous pyelograms and cystoscopy with ureteral catheterization and culture of the kidney specimens, as well as retrograde pyelograms, if necessary, to rule out obstructions or abnormalities. An attempt also should be made to rule out any infection such as urethritis, cervicitis or vaginitis, or disease of the gastrointestinal tract.

Treatment

Twenty-five years ago the only available antiseptic for treatment of the urinary tract was methenamine. Since then, the ketogenic diet, mandelic acid, the sulfonamides, nitrofurantoin and various antibiotics have been used. The clinical results obtained with the newer chemotherapeutic and antibiotic drugs are highly favorable in cases of acute infection. In chronic and recurrent infections they have not been as successful as first reported. These results have been shown in studies by Garrod, Shooter and Curwen[2] of 1000 cultures from 686 patients who had been treated and followed; by Rhoads, Billings and O'Conor,[3] and by others. In acute uncomplicated infections, treatment with methenamine, methenamine mandelate or the sulfonamide drugs is highly effective, costs less, and causes fewer reactions than the newer drugs.

The sulfonamides are of great value and are probably the drugs of choice for acute infections of the urinary tract. Toxicity, the most important consideration in choosing a drug, is greatly reduced with the newer sulfonamides. Most of these sulfonamides effect about the same pattern of response. The newer low-dosage, prolonged-action sulfonamides are probably as effective, but there have been reports of agranulocytosis with sulfamethoxypyridazine, which has several trade names, e.g., KYNEX® and MIDICEL®.

Mandelic acid, methenamine and methenamine mandelate are useful because of ease of administration, relative lack of toxicity,

and effectiveness against a broad range of bacteria. They can be given over a long period in chronic cases with some relief and without the emergence of resistant strains. Disadvantages of their use are gastrointestinal symptoms and hematuria. In addition, these drugs depend entirely on proper acidification of the urine; the urine pH should be below 5.5 or these drugs are not effective.

The antibiotics are highly effective in the treatment of acute uncomplicated infections. They are the drugs of choice in chronic recurrent infections, although the results leave much to be desired. When antibiotic therapy is used, cultures and bacterial sensitivity tests should be done and the appropriate drug should be used in the proper dosage for a sufficient length of time. It is better to vary toward the maximum rather than the minimum dosage. An adequate dosage is 2 gm. per day for 14 days, if tolerated. It is important to consider the toxic reactions which can occur with any of the antibiotics. These reactions include dizziness, headache, fever, nausea, vomiting, flatulence, abdominal cramps and diarrhea. If there is impaired renal function, the blood concentration can reach high levels, accompanied by irritability of the central nervous system, convulsions, shock, and even death.

Penicillin can be neurotoxic, both peripherally and centrally. It may cause noninfectious glossitis; stomatitis; many allergic reactions, mostly cutaneous; and a serum sickness type of fever 7 to 14 days after administration, with malaise, rash and lymphadenopathy. Penicillin has been useful in the treatment of gram-positive organisms, particularly staphylococci, streptococci and enterococci. Its usefulness is steadily decreasing, however, as resistant strains become more numerous, particularly in patients who have been hospitalized recently or who have undergone instrument examination.

Streptomycin and dihydrostreptomycin may be nephrotoxic and may produce vestibular damage and a severe epidermal reaction. The activity of streptomycin increases with each unit increase in pH; therefore, it is important to administer an alkali along with the streptomycin. Streptomycin has been particularly useful in treating staphylococcal and enterococcal infections; its greatest usefulness is in the treatment of renal tuberculosis. Its use is limited because of its ability to cause drug resistance, and, except under unusual conditions, it should not be used for more than four or five days.

Chloramphenicol (CHLOROMYCETIN®) may be hepatotoxic and may produce hematologic complications, but it causes fewer intestinal symptoms than any of the other -mycin drugs. Sensitivity tests show a great number of organisms sensitive to this drug.

Tetracycline (ACHROMYCIN® and TETRACYN®), oxytetracycline (TERRAMYCIN®) and chlortetracycline (AUREOMYCIN®) can be enterotoxigenic, causing nausea, vomiting, cramps and diarrhea. Severe stomatitis, vaginitis and proctitis may follow its use. Staphylococcal diarrhea, one of the most serious complications of antibiotic therapy, has been reported with these drugs, probably more frequently than with the other -mycins. These drugs act similarly on given bacterial strains, but this action can best be determined by sensitivity tests.

The bacterial reaction to erythromycin is similar to that of penicillin. It is useful against organisms resistant to penicillin, principally in the staphylococcal and enterococcal infections. It is less toxic than some of the other drugs.

Polymyxin B sulfate, neomycin and bacitracin are nephrotoxic and have little use except in unusual or complicated infections in which no other drug has been helpful.

Kanamycin sulfate (KANTREX®) is extremely effective in treating patients who have urinary infections. It has a wide antibacterial spectrum and has been useful in a variety of antibiotic-resistant infections. In most of the cases that showed no improvement, the organisms were found to be *Pseudomonas, Proteus* and enterococcus. Kanamycin should be given intramuscularly in treating urinary tract infections. The toxic effects are renal irritation with red and white blood cells in the urine, albuminuria, and an increase in the blood urea nitrogen. Also, eighth nerve dysfunction and

skin eruptions have been reported following the use of this drug.

Novobiocin (CATHOMYCIN®) can be given orally and has been most useful in treating staphylococcal infections.

VANCOMYCIN® should be given parenterally. It can cause renal irritability but has been used successfully in treating gram-positive organisms which have been antibiotic-resistant.

Nitrofurantoin (FURADANTIN®) is not an antibiotic and is effective against a high percentage of acute infections, and also against some persistent chronic infections which are resistant to other drugs. A comparatively high percentage of patients receiving this drug have complained of gastrointestinal disorders such as nausea and, less frequently, vomiting.

There is little evidence that combinations of antibiotics have value, with the exception of penicillin and streptomycin, and penicillin and the sulfonamides. Usually, combining drugs tends to foster the development of more resistant strains of bacteria and to increase the chance of toxic or allergic reactions.

I believe that antibiotics should not be used routinely in infections of the urinary tract. Instead, when there is a good indication, one should select the proper antibiotic after urine cultures and sensitivity tests are made. Before antibiotics are used for infections of the urinary tract, the choice of drugs should be the sulfonamides, methenamine mandelate and Furadantin.

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Although the use of insulin has greatly reduced surgical risk, the diabetic patient remains an operative challenge. Dr. Bothe describes preoperative technics in elective and emergency situations, stressing the importance of thorough laboratory examinations and proper diabetic management. Even emergency operations should be temporarily postponed if diabetic acidosis is encountered, but this and other problems peculiar to diabetic patients can be overcome by cooperation between surgeon and medical consultant.

Surgical Procedures in the Diabetic Patient

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THE use of insulin for the past 35 years has greatly reduced the surgical risk for the diabetic patient. More recently this rate has been further reduced by the use of the newer types of insulin and the discovery of antibiotics. With our greater concepts of values of micronutrients and by understanding the importance of and applying good nutritional and metabolic balance, the surgical risk in the diabetic patient is no greater than that which is indicated by the status of his cardiovascular-renal system.

We have known for years that certain conditions which necessitate surgery develop in diabetic persons because of the nature of their disease. While these conditions still do occur, in our experience they are diminishing in number. Carbuncles are not seen as often as they were in the past because of the early and active use of the antibiotic drugs. Gangrene develops less frequently, because the improved hygienic care and the dietary regimen of the present-day diabetic patient postpone the development of atherosclerosis for many years; at times, they may prevent occurrence of gangrene. Because of this, these persons are living longer; many of them come to the surgeon for operations which previously would not have been attempted; they have a pattern of disease and indications for surgical relief not unlike that of nondiabetic persons. This statement is predicated on the supposition that the diabetes is well controlled and managed carefully through the preoperative and postoperative periods. It also presupposes a close cooperation between the medical consultant and surgeon in regard to the preoperative and postoperative care and in agreeing on the ideal time for operation and even the type of operation contemplated. Neither one nor the other should attempt to manage both the operation and the diabetes. If the diabetes has not been properly treated, the diabetic patient of today is still a poor surgical risk.

Infection is of utmost concern in the diabetic patient who requires surgery; its location is of greater importance than its severity. Infections around the head and neck, as, for example, abscessed teeth, peritonsillar abscesses and the very occasional mastoid infection, are much more apt to produce a disturbance in a patient with recognized diabetes. Oftentimes,

in a person with undiagnosed diabetes, acidosis may develop before the diabetes has been diagnosed. Respiratory infections also seem to influence the diabetic state, but not so markedly; infections in the abdomen, which will be discussed subsequently, seem to be well tolerated by the diabetic person.

Even though this paper is primarily concerned with the surgical procedures in the diabetic person, a few words about the diagnosis of diabetes are in order. Any patient who shows glycosuria should be considered to have diabetes until it is proved otherwise. A simple screening test is to do a blood sugar determination two hours after the patient has eaten a meal containing at least 75 gm. carbohydrate; this value should be no higher than 100 mg. per 100 cc. as determined by the Folin-Wu technic. It is very rarely necessary to do a glucose tolerance test if the level of postprandial blood sugar is determined. The incidence of diabetes in the population of the United States is about 2 per cent, and it is much greater than this in middle-aged women.

Management

Diabetic patients in whom surgical intervention is necessary may be classified in two groups: those who need emergency operations and those in whom the surgical procedure is one of election. The latter group composes the majority of patients requiring surgery.

Method in elective operations—Our routine of handling the preoperative and postoperative care of the diabetic patient admitted for an operation of election is as follows: We like to have this type of patient admitted 24 or 48 hours before operation for reappraisal of his diabetic status. In such a survey, we do a blood urea nitrogen determination, urinalysis, urea clearance, if indicated, and an electrocardiogram. Retinoscopy is done on all diabetic patients admitted, which may give one an early lead as to the possibility of a low kidney reserve or an early Kimmelstiel-Wilson picture. A diet approximate to that of the nonsurgical patient is initiated. The diet depends on the physical build of the patient, but it usually contains from 150 to 200 gm. carbohydrate, 70 to 90 gm. protein, and approximately 80 to 90 gm. fat. To keep the blood sugar level around 130 to 150 fasting, we continue the type of insulin preoperatively that the patient has taken at home. We are more satisfied if the blood sugar level is not below 100 and if it does not approach hypoglycemic levels before operation.

The day of operation, we divide the insulin into four equal doses. We estimate the total amount of available glucose in the diet, using the old Woodyatt and Shaffer formula, and divide this carbohydrate into four equal portions. If the patient has been taking a long-acting insulin, we transfer him to regular insulin. Three hours before operation, schedule permitting, the patient is given one quarter of his total dosage. Three hours postoperatively, blood is taken for a sugar and carbon dioxide determination. The patient again is given another quarter of the carbohydrate and another quarter of the total insulin. If it is the surgeon's routine that the patient receives intravenous glucose postoperatively or some of the preparations containing protein and a certain amount of glucose, we attempt to have that estimated in the total carbohydrate intake for the day. The other two quarters of the carbohydrate are administered at six hour intervals, and the dose of insulin depends on the postoperative chemistry.

Here again we are not anxious to drop the blood sugar to a low level. We are more interested in whether or not ketosis is present. If the blood sugar is satisfactory, we continue with the same insulin dosage. The first postoperative day, the patient is usually given a liquid diet, and in the 24 hours he receives the same total amount of glucose given preoperatively and a dose of regular insulin with each feeding on a three hour feeding schedule. The postoperative program depends somewhat on the operation done and on the surgeon's routine. However, usually in 24 or 36 hours the patient can be given a liquid diet and from that shifted to a soft diet, still with regular insulin and with fasting blood sugar and blood sugar determinations done at 4 P.M.

We believe that this is a safer procedure than attempting to carry patients through surgical procedures with a long-acting insulin.

There has been some discussion and, possibly, disagreement about shifting the patient to a short-acting insulin during his preoperative and postoperative periods, if he had originally been standardized on long-acting insulin. It is important to remember that many surgical procedures are done for the relief of infection or the release of encapsulated pus. Very often following this relief of infection, the insulin requirement drops rather suddenly. It is safer to have a postoperative blood sugar level somewhere above 150, particularly in the elderly or middle-aged diabetic patient, than one around 70 or 80, as this is a much safer buffer for the coronary circulation and the myocardium. We also wish to control the blood sugar within several hours postoperatively by the administration of regular insulin or glucose, as indicated. If necessary, the postoperative blood sugar can be balanced, and the fear that the long-acting insulin will produce hypoglycemia in 18 or 24 hours is not a serious source of worry. As soon as the patient can tolerate a fairly good diet, he again may be given long-acting insulin, often within 48 hours after operation. After intestinal or brain operations, the patient often is fed intravenously for days, and the glucose intake is balanced with frequent doses of regular insulin. Repeated blood chemistry studies must be made to avoid hypoglycemia or acidosis.

In some patients who have encapsulated pus, extensive infection which has not responded to antibiotics, or gangrene with infection it is often impossible to reduce the blood sugar to a so-called normal level. As long as the patient is free from acidosis, palliative surgical procedures can be performed, and if indicated, more extensive operation can be done later. Such a patient is much easier to control after the surgeon has relieved the infection. With the newer drugs, one does not see this type of patient too often, but when encountered, he presents a real problem.

Method in emergency operations—In considering emergency surgical procedures in the diabetic patient, it is very important to remember that the symptoms of diabetic acidosis mimic those of an acute intra-abdominal lesion. They are nausea, vomiting, abdominal pain (at times associated with localized areas of tenderness), leukocytosis which may run anywhere from 12,000 to 40,000 leukocytes, dehydration and fever.

Two patients who recently were admitted to the Abington Hospital in the same day are of interest. One patient, known to have diabetes, was referred to the medical service because of rather vague abdominal pain. This patient was found to have an appendiceal abscess, confirmed at operation. The second patient, in whom diabetes was not diagnosed, was admitted to the surgical service with the diagnosis of an acute condition within the abdomen, requiring surgery. Preoperative laboratory studies revealed that this patient had diabetic acidosis; his symptoms disappeared with appropriate treatment for that entity.

It is interesting that 20 years ago 20 per cent of a series of 240 consecutive patients with acidosis were admitted on the surgical service with the diagnosis of an acute condition within the abdomen. It is a great credit to the surgeons that only one was operated on, and that was done under somewhat unusual circumstances. In a comparative survey, which was made only three years ago, the number of patients with acidosis who were admitted directly to the surgical service was down to 5 per cent. This seems to indicate that the care of diabetic patients by the family physician has improved; it also indicates physicians are recognizing the possibility that diabetic acidosis presents a clinical picture difficult to differentiate from an acute abdominal condition.

Even though a patient does have a condition requiring surgical intervention, as well as diabetic acidosis, the acidosis is certainly a cause for postponing operation. Hemorrhage and laryngeal obstruction are the only conditions which would require immediate operation in the presence of acidosis. Within just a few hours the diabetic acidosis can be controlled to a degree at which a more proper appraisal of any underlying pathology can be determined. The patient also will be a much better risk if he does not have ketosis, particularly if an abdominal operation is needed.

Beardwood and I[1,2] reported several series of acute intra-abdominal lesions found in dia-

betic patients and pointed out that the clinical picture was much milder than in the nondiabetic patient with a similar pathologic condition and was much milder than the abdominal picture seen in the well-advanced case of diabetic acidosis. Acidosis has developed in very few of our patients, even those with abdominal conditions such as acute appendicitis with abscess, an acute condition of the gallbladder, and gangrene of the bowel. The leukocytic and fever response in these patients is markedly diminished in lesions of the peritoneal cavity. We often find that acidosis may develop in a patient with an abscessed tooth but not in a patient with an appendiceal abscess. We now have a series of 64 diabetic patients with acute conditions within the abdomen in whom the picture was so mild that the surgeon was tempted not to proceed, believing that the condition was subsiding. Thus, the unusual situation of finding a medical man urging a surgeon to operate, the surgeon being unwilling, is indeed a very rare one.

The cause of the abdominal symptoms in acidosis is not known. It has been postulated that they possibly may be due to pancreatitis, but certainly the patients we have studied have shown no abnormality of their pancreatic function either during or subsequent to the attack of acidosis. At times there may be profound hypochloremia associated with the pain, which is not necessarily confined to the abdomen but may occur in the thighs and groins as well.

When a diabetic patient is admitted for an emergency procedure, we immediately do blood sugar and carbon dioxide determinations. If the patient is not acidotic, 50 gm. glucose in a 50 per cent solution is administered intravenously along with a dose of insulin which depends somewhat on the previous insulin dosage that the patient has received. If the patient has not taken insulin, we usually give 5 to 10 units with the intravenous injection to carry him through the immediate surgical procedure. We again check his chemistry three hours postoperatively and administer 50 gm. glucose every six hours or 200 gm. glucose in 24 hours, given either orally or intravenously. The dose of insulin subsequent to surgery depends on the postoperative chemistry. The number of our diabetic patients who require immediate operation is relatively small.

A fair number of patients with acute glaucoma require immediate, relatively minor surgical procedures. No particular preoperative preparation is necessary, because chemistry studies can be obtained within an hour postoperatively and diabetic management carried on from there. There are a large number of cataracts in diabetic persons. In removing cataracts, intravenous glucose is better than oral feeding preoperatively and during the first postoperative 24 hours, as it obviates vomiting and nausea, which often cause a rupture of the operative site and hemorrhage into the eye.

For many years diabetic gangrene, with or without extensive infection, was a very serious complication and the cause of many deaths. As previously mentioned, we do not see gangrene to nearly the degree we did only 10 or 12 years ago. This is due to the fact that we do insist on and teach foot hygiene in our clinics as well as in our private practices; in this way we can warn patients that any break in the skin or any infection can lead to further trouble. Certainly it is important in the preliminary examination of diabetic patients and later, at intervals, to examine the feet for color, temperature and the presence or absence of pulsation. If this is done it is often possible to anticipate a gangrenous process before it occurs and, with care, to prevent its development. Diabetic gangrene is initiated usually by some relatively minor trauma to the feet; in a great many instances it is caused by a break in the skin resulting from epidermophytosis and the subsequent development of infection in tissues ill prepared to handle it. From the standpoint of treatment, possibly the most important phase is its prevention. Hygiene of the feet plays a very important role.

Diabetic gangrene is still a surgical problem. Because it is rarely seen in the upper extremity, this discussion will be confined to its occurrence in the lower extremity. In some patients in whom diabetes has been well controlled the gangrene can be treated by conservative surgery, thus decreasing the need for radical amputation.

In a series of patients requiring midthigh amputation, mercury was injected into the vascular tree of the amputated extremity at what had been the patient's mean blood pressure. A roentgenogram was then taken of the injected specimen. There were a number of findings of interest in this study, but I will enumerate only a few in this discussion.

In the patients who had had diabetes for a long time before gangrene developed, a rich collateral circulation had developed which was adequate to control infection and permit the surgical intervention to be conservative; the extremity was saved with the removal of only one or more digits. McKittrick used the transmetatarsal amputation in these cases, and his results are known to us all.

On the other hand, if the patient had had diabetes for only a short period before gangrene developed, the process usually was uncontrollable. Surgical procedure had to be radical, and our injected specimens showed there was little or no collateral circulation which would have helped to control the infection. In patients in whom gangrene developed in the heel, injection of peanut oil in the vascular tree of the amputated extremity showed that the posterior tibial artery was blocked far up in the leg, and in all injected specimens there was practically no collateral circulation. This condition occurred in some patients who had had diabetes for many years. In this study we were able to demonstrate that the intimal lesion of atherosclerosis in the diabetic patient is segmental in character, a fact which we had suspected previously. This should lend support to the thought that a venous graft could bypass the narrow portion of the vessel and could be helpful if the peripheral circulation is adequate. We believe this procedure may have merit. It has been attempted in one patient by Roberts, but, unfortunately, it was not successful. This should not deter us, as we still believe it is of value in properly selected cases. Our experience with sympathectomies in patients with diabetic gangrene has been far from successful. From the injected specimens, it seems to us that nature has already produced the maximal dilatation.

When is a diabetic patient ready for operation? We believe the important indication from a chemical viewpoint is that the patient not be acidotic, that his carbon dioxide level or other factors determining the presence of ketosis approach or equal normal values. The height of the blood sugar is not of too great importance, provided it is somewhere within reasonable limits. Surgical intervention is tolerated well in patients with a blood sugar level of even 250 or 300; in fact, at times, it is difficult to reduce the blood sugar level to normal until after the surgeon performs the operation. Preoperatively, our patients are studied to determine the cardiovascular-renal function and reserve. The results of these studies determine the operative risk and indicate the need for supportive care. ORINASE® should not be used in the preoperative and postoperative care of the diabetic patient. It is inadequate to control diabetes in the presence of infection or in the traumatic cases.

TABLE 1

SURGICAL PROCEDURES IN DIABETIC PATIENTS ADMITTED TO FOUR PENNSYLVANIA HOSPITALS FROM 1950 TO 1956

HOSPITAL	ADMISSIONS	SURGICAL PROCEDURES
Presbyterian Hospital	1,819	316
Graduate School Hospital	1,096	507
Abington Memorial Hospital	1,841	459
Jeanes Hospital	468	64

Table 1 shows the number of surgical procedures performed in diabetic patients admitted during a six year period to Presbyterian Hospital in Philadelphia, where undergraduate medical teaching is done, the Graduate Hospital, the teaching hospital of the Graduate School of Medicine of the University of Pennsylvania, the Abington Memorial Hospital, a large suburban hospital, and Jeanes Hospital, a small suburban hospital. These figures represent a fair cross section of the type of surgical experience one would have in diabetic patients. In the Graduate School Hospital, almost 50 per cent of all the diabetic patients admitted needed operations. This fig-

TABLE 2

SURGICAL CONDITIONS TREATED IN DIABETIC PATIENTS

CONDITION	NUMBER OF PATIENTS TREATED IN HOSPITALS				TOTAL
	Abington	*Presbyterian*	*Jeanes*	*Graduate School*	
Malignancy	54	46	9	105	214
Pancreas	1	3	1	5	10
Uterus	16	9	2	6	33
Gangrene	37	50	10	33	130
Cholecystitis	36	22	5	26	89
Carbuncles	19	2	1	10	32

ure is out of proportion in comparison with the other hospitals, as this institution has very active eye and gastrointestinal services.

In our series, there were 5,224 diabetic patients seen in those four institutions from 1950 to 1956 inclusive. Of these patients, 1,346 required operations. It would be of little interest to give a detailed analysis of all the surgical conditions handled in this survey; thus the discussion will be confined to four groups of conditions treated: malignancy, cholecystitis, gangrene and carbuncles (table 2). Of the 1,346 patients, 214 (16 per cent) had malignancies. Ten of these malignancies occurred in the pancreas. Often this condition is attended with elevation of the blood sugar and a mild diabetic state. There is some evidence that carcinoma of the body of the uterus is much more frequent in diabetic persons than in nondiabetic persons. We found that over half of the 33 uterine carcinomas were in the body of the uterus. We were frankly surprised to find that 130 (10 per cent) of the patients in the series had gangrene, because gangrene is a much less frequent complication than it was years ago. We have not broken down these 130 cases for this discussion, but we have found in recent years that the majority of patients with gangrene either did not know they had diabetes or were not very intellectual or cooperative in managing their diabetes.

The incidence of 32 cases of carbuncle was not expected in view of the wide and early, almost promiscuous, use of antibiotics for any pyoderma that exists. The mortality rate in this particular group compared favorably with that in a similar series of nondiabetic patients. The association of cholecystitis with diabetes has long been recognized; in our series, 89 (7 per cent) of the patients who had operations had cholecystitis or cholecystitis with lithiasis. There were two cases of malignancy of the gallbladder.

Comment

The diabetic patient who requires an operation is a challenging problem; there is no phase of medicine in which teamwork between the surgeon and the endocrinologist is of greater importance than in the management of such patients. Many diabetic patients will go through operations without much difficulty, but in a large number electrolyte imbalance and difficulties will develop which make the operative procedure a more risky one, and morbidity of recovery of these patients is proportionately higher than of the nondiabetic patients. I wish to state again that the diabetic patient is no greater risk operatively than the condition of his cardiovascular-renal tree, if given thorough evaluation by laboratory examinations and sufficient time for proper diabetic management.

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Self-help Devices:
Grasp and Holding

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EDITOR'S NOTE:

Each year many persons in all age groups become disabled in varying degrees as a result of illness and accident. With proper treatment and the help of specially designed devices, many such persons can achieve partial or complete independence in the everyday aspects of living and working. Great progress in understanding and in answering the needs of disabled persons has been made through the devoted efforts of Dr. Howard A. Rusk and his associates at the famed Institute of Physical Medicine and Rehabilitation of New York University-Bellevue Medical Center. A general research program in self-help devices has been supported for the past eight years by the National Foundation, from which more than 2500 devices have evolved. Since 1956, a special section has been established for the arthritic patient by the Arthritis and Rheumatism Foundation.

POSTGRADUATE MEDICINE here presents the first of a series of features describing and illustrating many types of devices which have been developed and tested at the Institute to help persons with different types of disabilities gain a greater measure of usual living. This material is being especially assembled for POSTGRADUATE MEDICINE by Dr. Edward Lowman, Director of the Arthritis Self-help Device Office of the Institute of Physical Medicine and Rehabilitation of New York University-Bellevue Medical Center.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

SELF-HELP devices are often the bridge between dependency and independent living. They should not replace the intelligent use of therapeutic measures which may remove an existing disability. They can, however, compensate for impediments which therapeutically present an impasse, and when used discriminately often are the means of reopening wide new vistas of independence and self-reliance.

In this and subsequent issues will be illustrated devices which for the most part are easily available, simple to operate, and reasonably priced. Suggestions for home-devised aids will be offered when there is no known commercially available unit, or as substitutes. At times it will be important to include devices which may be beyond the financial means of the average purchaser. Whenever possible the patient is urged to seek competent medical opinion before purchase of a seemingly expensive device.

Inclusion here does not constitute an indorsement of a product, but it does imply that each unit has been tested at the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center and proved to offer some degree of help to the disabled.

As eating and drinking are basic activities of daily living, considerable research in adaptive equipment has already been done in this area, and today there are more commercially available devices than can be covered in one issue. This article will deal with aids to assist *grasp and holding*, as differentiated from devices for reaching and withdrawing from the mouth, single-hand cutting of food, and stabilizing the plate. Aids for *drinking* will be covered separately.

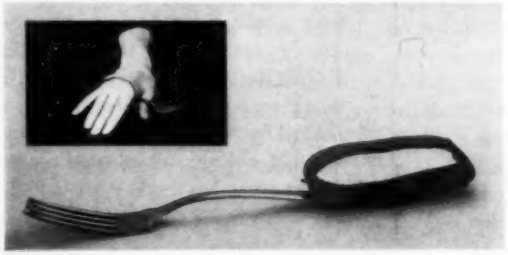

FIGURE 1. Cuff of elasticized webbing to fit over metacarpals of the hand, and doubled strip of leather with opening to fit handle of an eating utensil. Available from Fascole, 229 Fourth Avenue, New York City, or easily made at home.

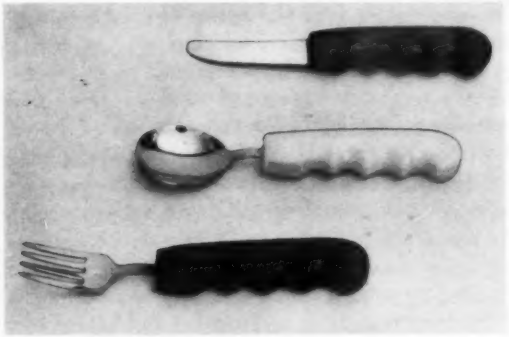

FIGURE 2. Indented plastic handles for either right- or left-handed use. Each unit costs about $2.00. Available from J. A. Preston Corp., 175 Fifth Avenue, and Fascole, New York City.

FIGURE 3. Although most built-up handles will aid grasp, materials used should not appreciably increase total weight of the device. These handles are made of lightweight wood. Pegging can be removed easily in instances where it is found to be a hindrance. Manufacturer has also designed several handles which are longer and jointed for more comfortable approach to the mouth. These will be shown in the next issue along with aids for reaching the mouth when there is limitation of motion affecting this activity. Cost of devices shown is approximately $2.00. Available from Adjustics, Inc., 169 Thompson Street, New York City.

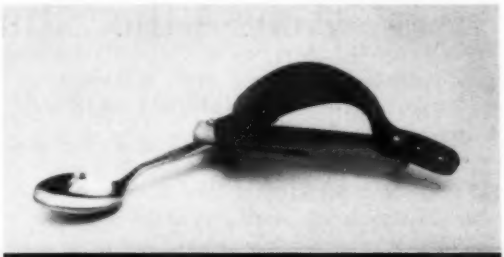

FIGURE 4. Leather cuff which can be affixed to plain-handled devices shown in figure 3 for persons having difficulty holding an eating utensil. Additional charge for leather cuff is $0.75. Available from Adjustics, Inc.

FIGURE 5. "Swivel or Sta-level" spoon remains level even with some overflow activity in the upper extremity. Spoon is also of value when supination-pronation of forearm is restricted. Bowl is stainless steel and handle is plastic. Cost is about $1.00. Available from J. A. Preston and Fascole.

FIGURE 6. "Teeny Poon" for children is made of soft pliable rubber which holds its shape. Children can bite down hard on it without danger of bruising lips. Spoon is lightweight and curved handle aids grasp. Packed two to a box in several colors, cost is about $1.00 per box. Available from Fascole.

The next article in this series will illustrate additional devices to help with eating problems with focus on aids for reaching the mouth when there is limitation of motion affecting this activity; special knives for single-handed cutting; a guard for keeping food from spilling off the plate, and devices for stabilizing food plates and bowls.

Although the pathogenesis of acne is better understood than it was 10 years ag , there are still divergent views on some of the facets involved. Hyperplasia, abno mal follicular keratinization and host susceptibility are considered the essenti l factors in the development of acne; however, the mechanisms governing the factors are still controversial. According to the author, individualized treatme t based on sound rationale is usually successful. The effectiveness of dermabrasio depends chiefly on the skill of the operator and the shape of the scars.

DISEASES OF THE SKIN—*Second of a Series*

Acne—the Situation at Present

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HERBERT RATTNER

ACNE is not easy to write about despite the fact that it is so common and readily recognized. This is so because there is so much about acne that is complex and unsolved. It is characteristically a disease of adolescence, yet on rare occasions it is observed in infants, and its appearance in the late twenties, thirties and even in the forties is not rare. We have come a long way in our understanding of acne in recent years, and we think now that we understand the pathogenesis. The present-day treatment is far superior to that of even a decade ago. Yet there are wide gaps in our knowledge of acne, and the need to fill them is great, for although there is no mortality with this disease and the morbidity from it is negligible, acne not infrequently literally ruins lives. To the unfortunate victim of a deep-seated, cystic, scarring acne, and to his or her family, the disease assumes utmost importance from both a social and an economic standpoint, for the acne victim has a decided disadvantage in both of these highly competitive situations.

Acne is, of course, a disease of adolescence. It is likely to be quite severe when it occurs in big, strapping, athletic boys. Acne does not occur in eunuchs or in persons rendered eunuchoid. Acne frequently flares up with the menses. The disease is likely to occur in girls with menstrual irregularities, but usually without any demonstrable endocrine disease. Acne often develops in older women who are being treated with androgen for one reason or another, and it may develop in women who have masculinizing tumors. It has been produced experimentally in girls by the administration of progesterone. For these various reasons, it is assumed that acne is essentially an endocrine disorder in the nature of an androgen-estrogen imbalance.

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In addition, it is a common observation that persons with acne have more than a normal amount of scaling of the scalp, and the scalp as well as the face is likely to be oily. Acne frequently develops on the forehead after the use of greasy or oily cosmetic preparations on the scalp. It may develop in young women who overdo the use of heavy face creams, and the disease is quite common in young men, such as machine shop workers, who in the course of their work are exposed to oils which they may carry to their faces with their hands.

The ingestion of bromides or iodides often produces acne lesions, and even foods rich in iodine, such as sea foods, may aggravate acne. Chocolate produces acne in many persons. Even milk, when ingested in large quantities, has been incriminated. Resting the chin on one's palm or friction from a rough collar or scarf often produces acne lesions, and the wearing of sweaters sometimes produces lesions on the back and shoulders.

Acne is likely to flare up as a result of emotional tension. It becomes worse on humid days when there is increased perspiration. Severe acne is encountered among troops stationed in humid tropics, and it is bettered by exposure to sunlight in a dry climate. Acneform lesions may develop in persons with manifest deficiency of vitamin A, and corticotropin or corticosteroids may induce acne. All of this would seem to indicate that acne may be influenced by any of a number of factors capable of promoting dysfunction of the pilosebaceous apparatus.[1]

Based on the foregoing clinical observations and fortified by the results of experimental studies,[2] a workable theory has been advanced to explain the pathogenesis of acne. In persons with a seborrheic habitus, usually adolescents, hyperplasia of the sebaceous gland occurs because of androgen-estrogen imbalance. The fluid secretion of the sebaceous gland increases in amount and becomes thickened; abnormal keratinization occurs; a plug is formed which is composed of jelled oil and desquamated epithelial cells; back pressure then develops in the duct; the gland enlarges, and a comedo forms. The plug acts as a local irritant, secondary infection sets in, and clinical acne develops. The changes may be deep-seated or superficial; the host's reaction to the changes and to the secondary infection may be sharp or sluggish, and it is this combination of factors that determines the character of the clinical picture, whether the acne is superficial, deep-seated, sparse or profuse.

Attractively simple as it appears to be, this theory of the pathogenesis of acne is, in certain respects, incomplete, and there are divergent views on some of its facets. There are those who believe that the production of acne is dependent on a combination of a hyperactive cholinergic function of the autonomic nervous system which causes hyperactivity of the sebaceous glands, and an insufficient number of arrectores pilorum to deal with the excessive amount of secretion.[3] Other authors[4] believe that there is an actual destruction of the follicular wall and an outpouring of the follicle contents leading to abscess formation. This is apparently what occurs in chloracne.

There is a lack of agreement whether the presence of hairs affects the development of acne. It has been postulated that, in a follicle subject to androgenic stimulation at puberty in such a way as to produce hyperkeratosis and seborrhea, temporary absence of an effective hair penetrating the mouth of the follicle will make the discharge of sebum and cellular debris so difficult that a comedo is formed.[5]

Other authors have maintained that the mere presence of hyperkeratosis is no proof that it is a major factor in acnegenesis. It is suggested that comedones form in pilosebaceous follicles in which the hair is rudimentary.[6] Seborrhea is present and follicular hyperkeratosis develops as a result of hormonal influences. The excess sebum attempts to flow through a narrowed hyperkeratotic channel. The rudimentary hair cannot force its way through to act as a drain for the sebum. At the same time the inadequate pilomotor muscles are unable to propel the sebum to the surface, and if the sebum is abnormal it may contribute to comedo formation. It is maintained that owing to androgenic action the wax content of the gland is increased and hardens

FIGURE 1. Acne confined to the chin of a patient who is in her 30s.

FIGURE 2. Mild acne.

readily and that androgenic influences also control the development of hyperkeratosis of the follicular pore which obstructs the outflow of sebum. More recently, it has been suggested that there may be a sebaceous gland-stimulating hormone in the pituitary gland, a sebotropic hormone.[7]

In short, there are probably a number of factors which influence the acne lesions—hyperkeratosis of the follicular opening and in the duct of the sebaceous glands, hyperactivity of the sebaceous gland, enlarged sebaceous glands, rudimentary hair, weakened musculature, etc. The role played by these various factors has still to be explained as does the mechanism by which such things as humidity, certain drugs and foods, iron deficiency anemia and external irritation influence the acne lesion. It has recently been contended that all these puzzling factors can be embraced by the concept of adaptation—that acne might well be a disease of adaptation.[8] It is an up-to-date theory, if not entirely convincing, and while there is agreement that the three factors, sebaceous gland hyperplasia, abnormal follicular keratinization and host susceptibility, are essential for the development of acne there is still uncertainty as to the mechanisms that govern them.

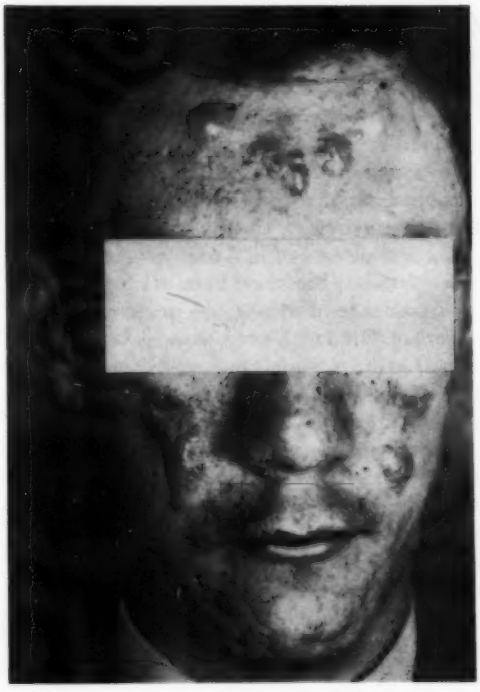
The Clinical Picture

Acne lesions occur on those areas of the skin rich in pilosebaceous structures, namely, the forehead, cheeks and chin (figure 1), the sternal region, the back, and the scapular and shoulder areas. In these areas, the skin is usually more oily and there are comedones and papulopustules, the necessary triad of symptoms for a diagnosis of acne. Fortunately, in most instances the lesions are small, few in number, and superficially situated. In such cases, the lesions may come and go with the menses or dry up on exposure to the sun, or they may disappear spontaneously. At the most, they constitute a slight annoyance and are looked on as part of the growing-up process (figure 2). Too often, however, the acne continues to progress and the lesions become sufficiently numerous to constitute a cosmetic problem (figures 3, 4 and 5), but, more im-

FIGURE 3. Moderately severe acne.

FIGURE 4. Indurated acne.

FIGURE 5. Cystic acne.



portant, the lesions may become deep-seated, persist for a long time and often produce scars.

The character of the lesion is determined largely by the degree of resistance or susceptibility of the host, and, since host resistance to infection and irritation plays such an important part in cases of acne, it is to be expected that the pictures presented by acne are extremely variable. In some cases, there may be only a few comedones and some scattered small papulopustules, while in others there may be deep-seated papules or cystic abscesses. The eruption may be exceedingly sparse, consisting of only two or three lesions, or it may be so profuse as to cover almost the entire face or only a part of it, as the chin or forehead. Lesions may be limited to the shoulders or to the chest.

In most instances, the inflammatory response lies between the two extremes of comedo acne and the cystic variety (figure 5). The host's response to the primary irritation of the comedo or to a true hyperallergic sensitivity to bacterial and other antigens in the follicular column, or both, may be minimal or

violent. If minimal, small superficial acne lesions result. When violent, indurated or cystic acne results, and it is these two varieties that cause scars.

Treatment

For nearly a century, a number of methods of treatment have been suggested for acne. Since knowledge of the basic or fundamental factors has not kept pace with clinical knowledge of acne, treatment is entirely empirical. It is based on rational empiricism which, although not ideal, is nevertheless highly effective in the majority of cases. Stated simply, it aims to lessen activity of the sebaceous glands and to combat infection; to accomplish these, it employs antibiotic drugs, estrogenic substances, steroids, roentgen rays, ultraviolet rays, dietary measures, toxoids and vaccines, vitamins, operation and, most important, topical remedies and psychotherapy. The last two measures, all-important in the management of acne if employed judiciously, are of the utmost value and offer the finest opportunities for artful practice of medicine.

Because of the variability of acne, there cannot be a routine treatment. For all patients, however, hygiene and dietary measures are the same. The skin of the acne patient is oily, not necessarily dirty, and often it is infected. The liberal use of ordinary soap, by frequent applications rather than by prolonged and vigorous scrubbing, effectively reduces oiliness and combats infection. The scalp should be kept clean and as free of dandruff as possible. For most patients, the liberal use of shampoo and the avoidance of greasy hair preparations are sufficient. Old-fashioned tincture of green soap is still an effective shampoo although it lacks the glamour of advertised brands. Girls prefer the latter.

It occasionally is necessary to institute treatment with lotions or ointments as for seborrheic dermatitis. The eating of sea food, due to its high iodine content, should be restricted, but the restriction of iodides need not be carried to the point of avoiding iodized salt, since in certain parts of the country such ingestion of iodides is necessary for teen-age patients. In rare cases, it may seem desirable to avoid chlorinated drinking water. It is well to restrict the use of foods that are hot, either in spice or temperature, for hot foods have a tendency to reflexly accentuate activity of the sebaceous glands. For the same reason, one should restrict the use of foods that are very rich in fats, foods such as chocolate, nuts, ice cream and sharp cheese, and, if pustular elements are prominent, restriction of carbohydrate intake should be recommended. All of these measures are of value but not of such paramount importance that insistence on them might result in malnutrition or in forfeiting the cooperation of the patient. It is best to explain to the youngsters the reasons for the dietary restrictions. With intelligent understanding, more and better cooperation is made possible.

Systemic treatment—Antibiotic drugs and corticosteroids are of distinct value in the treatment of deep-seated pustular or cystic acne. The tetracyclines appear to be far superior to penicillin or to the sulfonamides. Some physicians prescribe them for short intervals; others favor their administration for longer periods. The expense of the drugs and the possibility of untoward side effects place limitations on their use, but if these can be overcome the judicious use of antibiotic drugs is well worthwhile. Corticosteroids are also recommended by some physicians for acutely inflamed cystic acne lesions (figure 5). The rationale for the use of these drugs has been based on an assumed similarity between these lesions and the Shwartzman phenomenon. It is probably their anti-inflammatory effects that produce the favorable results. The drugs, like the antibiotics, are usually administered for only short periods to care for "acne crises," and they are administered in decreasing doses with full awareness of attendant complications, dangers and high cost.

Vaccines and *Staphylococcus* toxoids still have their advocates, and some physicians employ them routinely. Largely, however, they have been displaced by the antibiotic drugs, which are more effective. On occasion, either toxoid or vaccine administered intradermally in increasing doses seems to be beneficial in a case in which the response is sluggish. More

often than not, the administration of small doses of estrogenic substances for 10 days prior to the menstrual period is beneficial, but the same results frequently can be obtained by the premenstrual administration of diuretic agents such as ammonium chloride. Estrogenic substances are rarely used for males except experimentally. Since excessive sweating, which frequently is accompanied by excessive oiliness, seems to aggravate acne, anticholinergic drugs are sometimes prescribed.

Acneform lesions have been observed in persons whose vitamin A intake is deficient, and reports that acne has not been observed in Eskimos, whose diets are rich in vitamin A, plus the fact that this vitamin tends to exert a favorable influence on cornification at follicular orifices, have caused some enthusiastic recommendations for vitamin A therapy for acne.[9] It is difficult to evaluate the results, but certainly they are disappointing in the majority of cases—sometimes they appear to be favorable in cases of comedo acne or small follicular papular lesions. Water-soluble vitamin A is favored by those who employ it. Prolonged intake of large doses of this vitamin may lead to intoxication.

Since acne often improves as a result of exposure to sunlight, treatment with vitamin D has been recommended. Some physicians attempt to enhance its effects by adding vitamin B and ascorbic acid. The results are altogether equivocal.

Other measures may be necessary. These include the administration of thyroid substance when metabolism is low; the use of iron, liver or related substances when indicated; and encouragement of the patient to exercise sufficiently and to avoid constipation, fatigue and tension.

Topical treatment—For years, chief reliance has been placed on sulfur as a topical remedy. It may be used in the form of a drying lotion or an ointment, which usually is applied before the patient retires. Resorcinol and salicylic acid frequently are added. Lotions are preferred in the usual case, but a paste is more useful in cases of cystic acne. The following prescriptions have been found useful.

Prescription No. 1

Resorcinol	3.0%
Precipitated sulfur	5.0%
Neutracolor	1.5%
Zinc oxide	
Calamine	
Talcum āā	10.0%
Glycerine	
Alcohol (70%)	
Water āā q.s. ad	100.0%

Prescription No. 2

Zinc sulfate	4%
Sulfurated potassium	4%
Water q.s. ad	100%

Prescription No. 3

Precipitated sulfur	5%
Salicylic acid	3%
Zinc paste q.s. ad	100%

Many more "elegant" preparations are available. In addition to sulfur and resorcinol, some of these preparations contain antibiotic agents, hydrocortisone, and even estrogenic substances. In general, estrogenic products have not been well received. Since the aim of topical preparations is to produce slight dryness, erythema and faint scaling, the concentration of the various ingredients may have to be varied from time to time. In cases in which improvement occurs in the summertime, ultraviolet irradiation during the winter months is sometimes, but not always, beneficial. Youngsters frequently overdo this irradiation.

A very desirable procedure is the application of so-called cryoslush to the face when the patient is seen in the office. The slush is prepared by using a large mortar in which dry ice is pounded into a powder. Precipitated sulfur is added, and, finally, acetone is incorporated drop by drop while the mixture is stirred with a pestle until the slush is formed. The consistency should be just short of being watery.

An applicator made of gauze wrapped around a ball of cotton is dipped into the slush and then applied gently, without pressure, over the entire face by using a light wrist-movement touch. With each touch, there is a sizzling sound. The face is gone over three or four times, and after a few minutes the deposit of sulfur on the skin is removed with a dry towel. By that time, the skin has acquired

FIGURE 6. Flat scars of acne, which are most favorable for dermabrasion. a. Appearance before treatment. b. Appearance eight months after treatment.

a slight blush, is dryer and looks cleaner.

This is an excellent office procedure, for, aside from the improvement it produces, it is something that is actually done by the doctor, and this always pleases both the patient and the parent. To watch a witch's brew from a bubbling caldron being applied to one's face is an interesting and unusual experience.

The treatment requires regular visits to the office once each week for three or four trips, and then the interval between visits may be lengthened. The procedure enables the physician to observe a girl and to note whether there is a flare-up at a menstrual period. It offers an opportunity to observe the relationship between parent and child for evidence of tension; it promotes cooperation on the part of the youngster; and it permits changes, when necessary, from the routine treatment usually employed. It does not cure acne, but it is one of the measures used to help get the disease under control. It does improve the appearance, and it is far, far superior to the situation in former years when one saw a patient too infrequently and never really got to know him.

Roentgen therapy still has a useful place in the treatment of acne. In some cases it is the most effective method, but, because of the clamor against unnecessary ionizing radiation therapy in recent years, it is being used less and less. When proper technic is used by a qualified expert, it does not cause any damage or harmful effects, but how is one to answer the charge made by some physicists that such treatment is likely to be harmful to your children's children? Fortunately, in most cases, the skillful use of a combination of antibiotics, topical preparations, diuretics, cryoslush and, sometimes, ultraviolet radiation will keep acne under control.

Dermabrasion of scars—Unfortunately, in a still too large number of cases, the most ra-

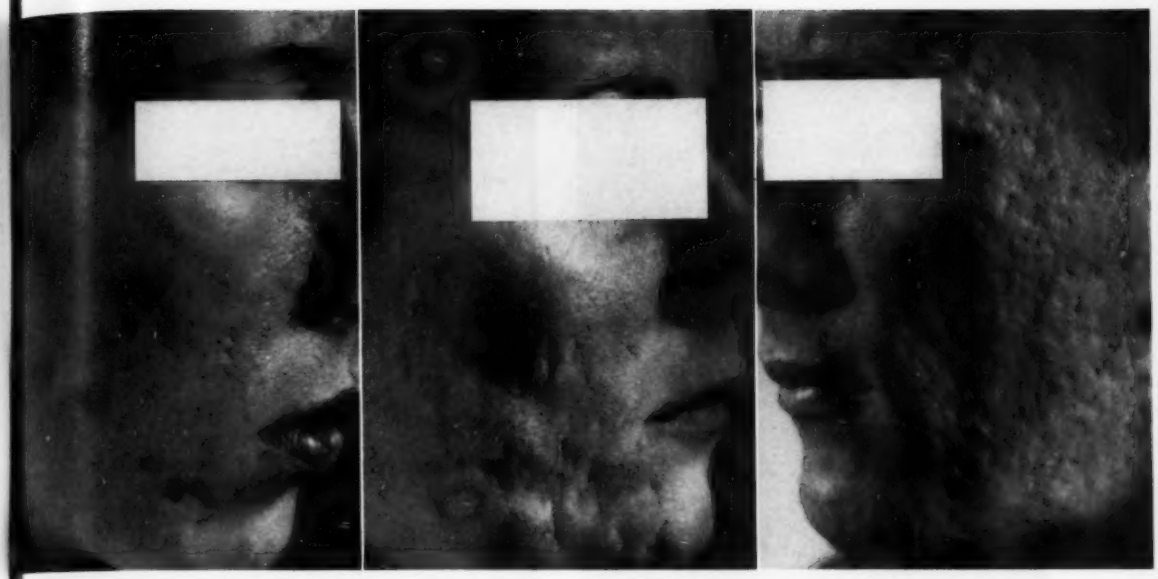


FIGURE 7. Results of treatment of scars that are not improved greatly by dermabrasion.

tionally devised scheme of treatment fails to produce improvement; lesions persist; new ones develop, and the patient ultimately is left with facial scars. Until recently, there was no effective way to treat such scars, but now, by means of dermabrasion, certain types of scars can be improved satisfactorily (figure 6).

In 1952, Kurtin described his method of refrigeration-abrasion which he termed skin planing. At first, some physicians resolutely refused to endorse the therapy, and others were enthusiastic about it to an unwarranted degree. The method has since been tried and accepted by many dermatologists throughout the country. Modifications have been introduced and experiences have been recorded. An adequate number of patients who have been treated by this method have now been observed long enough to permit an evaluation of the results.

Dermabrasion is new in technic only, not in principle. In the past, numerous measures were devised to eradicate acne scars, but all of them were found inadequate. These various methods included scarification, electrodesiccation, surgical excision, surgical shaving, chemical caustics, cryoslush therapy and mechanical abrasion by means of sandpaper, the most widely publicized method in recent years.

The planing method employs a refrigeration-type anesthesia that facilitates abrasion and also controls bleeding. It permits the treatment of small pits in areas such as the nasolabial fold. It is used in the office, for general anesthesia is not required.

The successful results of treatment depend a great deal on the skill of the operator and also on the depth and shape of the scars. Flat superficial scars (figure 6) respond better than do the deep-pitted, so-called ice-pick type of scars or the wide, flat, confluent scars which produce an undulating appearance of the skin (figure 7). Unfortunately, the latter types occur all too often and produce the most severe cosmetic defect, so that persons in great need of help obtain the least benefit. The results are seldom dramatic although, more often than not, patients are pleased with the cosmetic improvement (figure 8). In many cases, the improvement in the patient's well-being is so striking as to suggest that we have taken too lightly the importance of acne scars to the

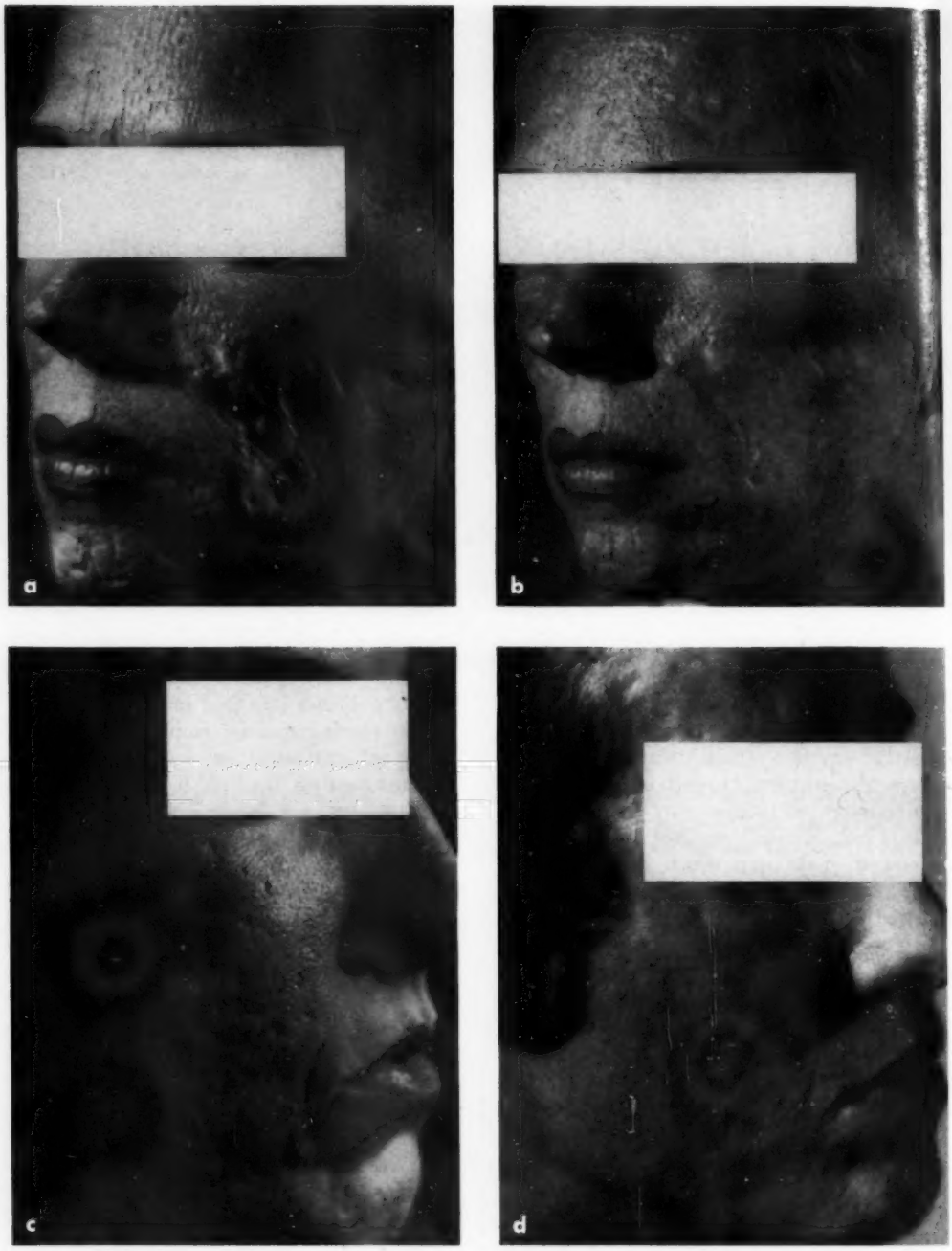


FIGURE 8. In each of these patients, the scars are improved, but there is very little change in the general appearance. a. Appearance before treatment. b. Appearance after treatment. c. Appearance before treatment. d. Appearance after treatment.

patient. The treatment may be repeated several times at intervals of six months if necessary. The age of the patient is not important, although results appear to be better in young persons. The presence of a few acne lesions need not interfere with the treatment. The complications from treatment that are occasionally observed are relatively unimportant. They consist of impetigo, milia, postoperative redness or hyperpigmentation, which may persist for several months, and, rarely, transitory eczematous patches.

Scars of recent origin apparently respond better to the treatment than do old scars. Scars on the chest, back, shoulders and neck do not respond as favorably to treatment as do scars on the cheeks. As with all cosmetic procedures, it is well, before treatment, to discuss the problem thoroughly with the patient in the presence of a relative and to stress, when thought necessary, that results will likely fall somewhat short of the patient's expectations. The whole experience will be more pleasant if the patient is sufficiently intelligent and emotionally conditioned to be content with improvement, even after two or three operations, rather than a complete cure, and, incidentally, it is tempting fate to try to foretell the amount, percentage-wise, of improvement to be expected from treatment. In general, only about 20 per cent of patients who inquire about dermabrasion have the type of scars that are suitable for the procedure.

Summary

The pathogenesis of acne is better understood today than it was a decade ago. The treatment today is far superior to what it was then. Sebaceous gland hyperplasia, abnormal follicular keratinization and host susceptibility are the essential factors in the development of acne, although there are divergent views about the mechanisms that govern these factors. Treatment, which should be individualized rather than routine, and which should be based on sound rationale, is successful more often than not. Dermabrasion for acne scars is helpful in certain cases, depending mainly on the shape of the scars.

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NEXT IN THIS SERIES

Cutaneous and Mucous Membrane Moniliasis

By EVERETT R. SEALE, M.D. AND J. B. RICHARDSON, M.D.

Illustrated in color

Natural childbirth is not a new practice; however, it is new to place the pregnant woman in an optimal psychologic milieu which enables her to use her innate physical and emotional powers to the fullest extent. Training for childbirth must be done only with the pregnant woman's permission and should include orientation of her obstetrician, her husband and all who care for her. In the author's experience, all women who have received education for childbirth have benefited from this instruction.

Training for Childbirth

HAROLD B. DAVIDSON*

Lenox Hill Hospital, New York

THE main objective of training for childbirth is to place the pregnant woman in her best possible emotional environment, thus enabling her to use her innate physical and emotional powers to the fullest extent. I favor training for childbirth as I favor the psychologic preparation of children and adults for such surgical procedures as tonsillectomy, hysterectomy, colostomy and so on. Such training should be, is becoming, and eventually *will* be part of the general cycle of a mental hygiene program. Preparing the new mother to be able to give her child a good emotional background should be a key point in this cycle.

HAROLD B. DAVIDSON

In addition to providing instruction in physical hygiene and exercises, this training substitutes fact for fantasy and mystery regarding parturition.[1] It gives the mother a chance to ventilate her anxieties in her classes or group work. It also gives the physician an opportunity to recognize the patient's particular psychologic needs. The important visit to the hospital before she is actually admitted and the ample moral support she receives complete the patient's preparation.

However, training only the patient is not sufficient. The obstetrician, too, must be oriented[2]—he must recognize and understand the mother's need for psychic hygiene as well as physical and reproductive hygiene. Her husband and all personnel who will care for her not only must be instructed in this program but also must be sympathetic to and cooperative with it.

For years there have been arguments as to what the term "natural childbirth" means. As Goodrich[3] has pointed out, it is wasted effort to continue discussions about a name; however, we must know what we are discussing.

Natural childbirth caused so much conversation and was objected to by so many people mainly because it was offered as a new system or method of obstetrics in many areas. It is *not* a new system,[4] but it is new to place the pregnant woman in a carefully planned, optimal psychologic milieu.[5] This concept is

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Adapted from a presentation before the fourth annual meeting of the Academy of Psychosomatic Medicine at Chicago.

not limited to any specific type of personality of either patient or physician. Partly through the anxiety-reducing function of group work, partly through the efforts of the physician and his personnel, and partly through positive transference to the physician for the duration of pregnancy and delivery, it enables the woman in labor to exchange a passively dependent emotional role for one in which she actively participates.[1]

All women are different, both physically and emotionally. Some tend to have rapid, spontaneous deliveries; others have prolonged, difficult ones. Some, who are emotionally and femininely mature, face their deliveries and the responsibilities of motherhood with joy and equanimity; others do so with varied, ambivalent feelings.[5] Many women, as a result of training and physical status, both wish and are able to deliver their babies without any or with only minimal medication and anesthesia. Some patients need and want full anesthesia of the "twilight sleep" type or its equivalent. (I might add that no matter what amount of anesthesia a patient wants or receives, a competent anesthetist is of vital importance in the delivery room.) It is essential that the woman have complete choice, and cooperation in her choice, of what she desires for the relief of pain. She must be made to understand that there is pain[2] and that there are situations in which anesthesia, at her physician's discretion, is essential for safe delivery;[5] but pain still is "what she feels"—the patient's reaction. Her interpretation of it depends on her entire emotional background—her childhood, development, reactions to her parents, attitude to being a woman and to menstruation and sex.[6] Her needs and reactions are controlled not only by education but also by psychodynamic forces.[6] Placing her in as near an ideal psychologic milieu as possible permits her to function best by proper, unconscious and free use of these powerful psychodynamic forces.

Above all, this training must be carried out only with the mother's permission. She should understand that the choice of her deportment in this situation is her own. This choice applies primarily to the amount or degree of medication or anesthesia, or both, that she will receive; but her permission also is involved in the acceptance or rejection of education or training for childbirth. This is not, as has been charged, a "negative process." Her decision is based on a *positive* approach to the realities of the situation.

We are all grateful to Dr. Read for introducing us to these possibilities, even though natural childbirth as first presented (and practiced by too many of its people) seemed to be a new method of obstetrics. It had many advantages, but (as too often practiced) was treated as a "cult" or an "ism," and in some instances it produced emotional trauma,[4] because the mother was unable to comply when put in a competitive environment. Great harm may occur when the patient is not allowed to control the amount of pain relief to be given, and when she is not treated on an individual basis. No woman in delivery should have to compete with other women or with an ideal simply to avoid medication.[5] Also, those who promulgate and teach this method (as practiced in some areas) tend to interpose themselves between the physician and his patient, thus robbing the woman of her greatest moral support—positive transference to her physician during pregnancy.

My original experience included psychologic studies and psychiatric interviews of my patients. All patients studied and reported on since the first report in 1953,[5] and after that, have been my private patients. All received education for childbirth. Many chose to have little or no premedication or anesthesia. I shall not quote statistics, but all the women who take this training get some benefit from it; some receive a great deal. Most of them manage so well with regard to the degree of medication and anesthesia required that I rarely need to resuscitate the newborn infant. My individual record of forceps deliveries, assisted breech presentations, cesarean sections, and so forth, generally approximates the standard statistics. An unexpected result of this training has been the greater ease with which births of babies in the occiput posterior and breech positions have been managed. When such situations are explained to the emotionally well-adjusted patient, she usually accepts the extra

time and effort required with notable equanimity and cooperation. She will recognize and comment on the discomfort or pain involved, but she does not exaggerate it or give way to panic. She can wait a long time for her medication without incurring emotional trauma. The fact that women soon forget the pain of labor has been recognized for centuries. Once labor is ended, these women exhibit a very real satisfaction in having helped themselves. We must never forget that it is the woman, and not the obstetrician, who delivers the baby.

Finally, I should like to state that although the obstetrician must be psychologically aware and alert, he cannot and must not try to play the part of the psychiatrist. There is still so much to learn about these reactions in obstetric and concurrent problems that it behooves us all, in educating or training for childbirth, to continue careful psychologic and psychiatric studies of our patients.

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Coming . . .

Self-help Devices:

Eating

Common Ocular Problems

Dan M. Gordon
New York Hospital-Cornell Medical Center, New York

Scientific Exhibit

Adapted from an exhibit presented at the 1958 annual meeting of the American Medical Association, San Francisco, California.

Introduction

THE more common eye conditions tend to cause redness, swelling, pain or loss of vision. When the cause of pain or loss of vision is neither obvious nor easily amenable to simple therapy, referral to an ophthalmologist is in order. Among the more refractory conditions are the uveitides (iritis, choroiditis, etc.) and the glaucomas.

Local ocular inflammations and allergies usually respond well to local and, at times, systemic corticosteroid therapy. Results of steroid therapy are poor in cases of herpes simplex, some exanthems, and the fungous infections of the cornea. One should be wary about using corticosteroids in any case of corneal inflammation (keratitis) in which the presence of the afore-mentioned conditions, especially the fairly common herpes simplex, cannot be definitely eliminated. Normally, the cornea has a mirror-like appearance. When this is absent and the cornea looks hazy, one should assume the presence of a keratitis until more precise examination proves otherwise.

Acute glaucoma is an ophthalmic emergency. Chronic glaucomas are classified on the basis of the appearance of the angles of the anterior chamber at gonioscopy, and are treated accordingly. The distinction by means of gonioscopy between open-(wide) and closed-(narrow) angle glaucomas simplifies management of the chronic cases. Those glaucomas secondary to other disease, such as iritis, usually clear as the underlying disease responds to treatment.

Among the most common and important ocular problems are

Inflammations

Allergies

Glaucomas

Results of therapy depend on

Accurate diagnosis

Usually indicates type of therapy

Availability of specific therapy

Depends on knowledge of etiology

Understanding the fields of action of therapy used

Knowing the mechanism of drug action

Proper route of administration insures medication reaching locus (e.g., topical route will not function when systemic route is needed, etc.).

"Tailoring" therapy to patient

Adjusting type and amount of medication according to patient's response

---

Use Enough —

Soon Enough —

Often Enough —

Long Enough

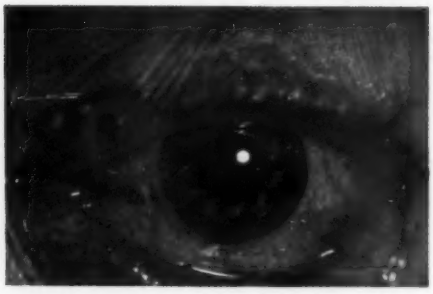
Corticosteroid Therapy Frequently Indicated

Inflammations

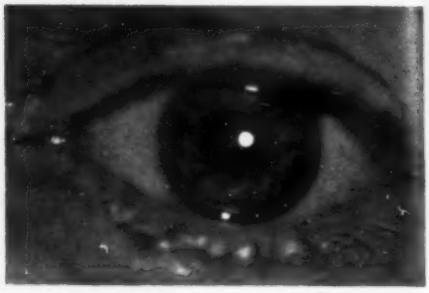
Conjunctivitis

Prednisolone 21-phosphate-neomycin sulfate (NEO-HYDELTRASOL®); topical only

Before



After three days

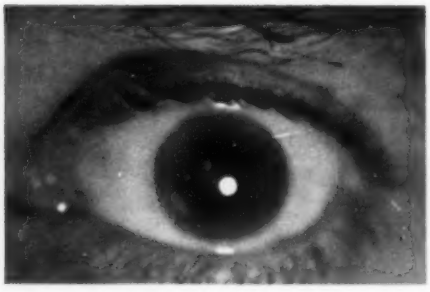


Episcleritis

Prednisolone 21-phosphate (HYDELTRASOL®); topical only

Before

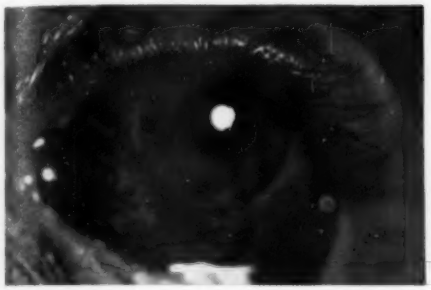
After 10 days



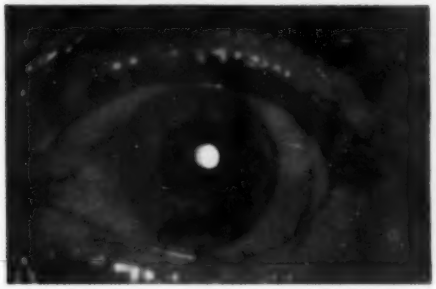
Iritis

Prednisone (DELTRA®), prednisolone (HYDELTRA®) or dexamethasone (DECADRON®); topical and systemic

Before



After two weeks



Choroiditis

Prednisone, prednisolone or dexamethasone; systemic only

Before

After six weeks

Allergies

Lid edema

Prednisolone 21-phosphate; topical only

Before

After four days

Vernal conjunctivitis

Prednisolone 21-phosphate; topical only

Before

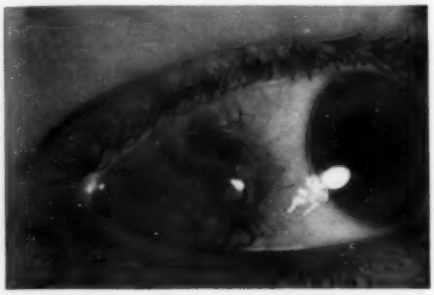
After 10 days

Granulation tissue

Retention granuloma

Prednisolone 21-phosphate and prednisolone 21-phosphate-neomycin sulfate; topical only

Before



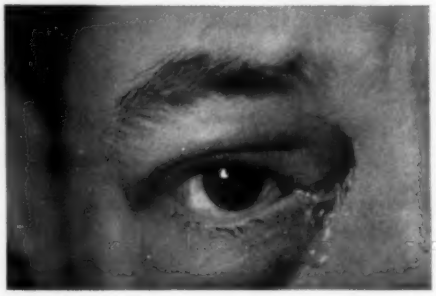
After eight weeks

Certain infections (Antimicrobials mandatory)

Severe meibomianitis

Prednisolone 21-phosphate-neomycin sulfate; topical only

Before



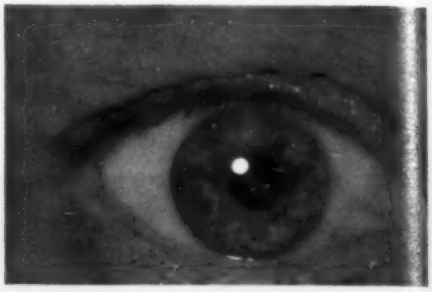
After five days

Limbal corneal ulcers

Prednisolone 21-phosphate-neomycin sulfate; topical only

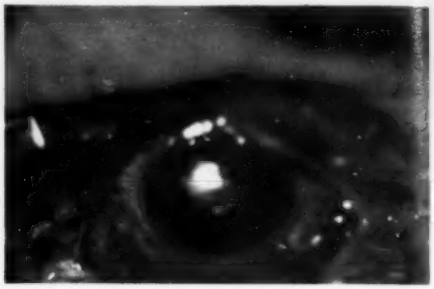
Before

After four days



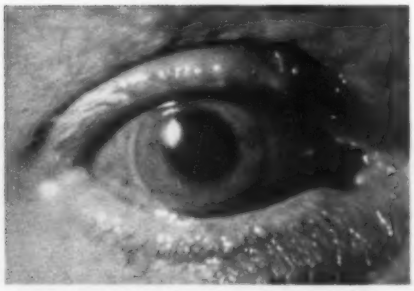
Contraindications to Steroid Therapy

Herpes simplex and ocular exanthems



Glaucomas

Acute



True ocular emergency
Miotics plus carbonic anhydrase inhibitors

Chronic

Gonioscopic view of angle of anterior chamber for accurate diagnosis

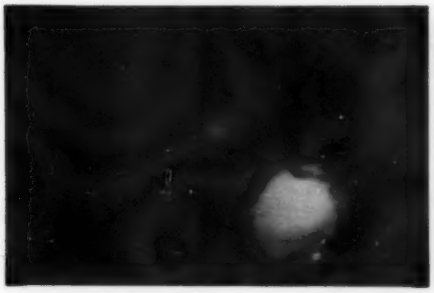
In chronic glaucomas, differentiation between a closed and an open angle by means of gonioscopy is important.

Glaucomas (Continued)

Closed angle

Miotics plus carbonic anhydrase inhibitors during attacks; miotics between attacks
Prophylactic peripheral iridectomy to prevent further attacks

Open angle



Chronic simple glaucoma, a progressive disease
Miotics constantly
If miotics fail to control, miotics plus carbonic anhydrase inhibitors

---

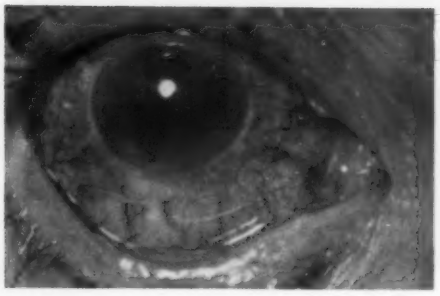
Open angle

Filtering operations when medical therapy fails to slow disease sufficiently
Rarely advisable before segmental field loss

Secondary glaucomas

When secondary to uveitis, condition is usually well controlled by adequate corticosteroid therapy (topical and systemic) plus carbonic anhydrase inhibitors.

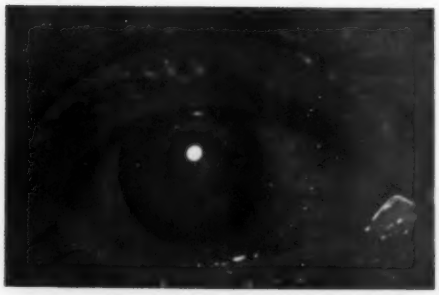
Before



Prednisolone 21-phosphate-neomycin sulfate
Prednisone; systemic
Dichlorphenamide (DARANIDE®)

After 15 days

Surgery rarely needed unless pupil is completely bound down.



When secondary to swollen lens, do cataract extraction. Use carbonic anhydrase inhibitor to prepare for surgery.

Glaucoma following lens extraction

DFP is miotic of choice. Carbonic anhydrase inhibitors may be indicated.

Surgery (usually cyclodialysis) performed when medical control fails.

Obesity: Diagnosis

JEAN MAYER*

Harvard University School of Public Health, Boston

I HOPE that previous articles in this series have laid the foundation for a better understanding of the physiologic basis of the development of obesity. The matter of caloric requirement is obviously fundamental to the analysis of the pathogenesis of disorders of energy metabolism. A caloric intake in excess of requirements eventually will cause obesity; a prolonged deficit will cause emaciation. The effect of the lack of physical activity on appetite, so often misunderstood and minimized, is probably the root of the slowly accumulating excess fat in many sedentary middle-aged persons who have no particular defect in the physiologic mechanism of the regulation of food intake and no psychogenic hyperphagia. Yet, these facts alone are quite insufficient to explain this most widespread condition. In fact, I am convinced that we can effectively treat obesity only when we recognize the extreme complexity of the problem. Hyperphagia and obesity may be common aspects of syndromes which have little in common otherwise. Before elaborating on a philosophy of treating the obesities, it may be pertinent to review recent investigations in the field of appetite and obesity, even though (as is true in the first stages of studying any disease or syndrome) most of the evidence is still largely experimental in nature.

To give an accurate picture of the subject of obesity, it appears useful to divide this presentation into three parts. The present discussion will reassess methods of diagnosing obesity. The succeeding article will deal with the etiology and pathogenesis of obesity, and the third will consider treatment.

Reasons for Diagnosing and Identifying Obesity

It may be necessary to recall that obesity is a problem for the practitioner. Although this statement may appear self-evident, it must be recognized that the majority of obese subjects view their obesity first of all as an aesthetic problem and sometimes as a moral problem or, at least, a problem in human relations. Obesity has been so derided that obese patients feel unattractive, and they are afraid of being considered sensual and weak. Most persons are motivated to place themselves on a diet or to ask for a reducing regimen because they are concerned with their appearance and with public opinion rather than with their health. If these were the only problems to be considered, one could well question

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whether it is the physician's function to devote time and effort to encourage and help weight reduction.

Actually, life insurance studies have clearly demonstrated that obesity is accompanied by increased mortality from a number of degenerative diseases. Dublin and Marks,[1] of the Metropolitan Life Insurance Company, deserve particular credit for establishing incontrovertible evidence of the association of obesity and disease. They have shown statistically that obese persons who reduce and stay reduced may substantially increase their life expectancy. Yet, at the same time, it is highly probable that the link between obesity and disease is more complex than the simple cause-and-effect relationship often suggested. To be sure, the excess fat in some persons is obviously dangerous per se. It increases surgical risk by making administration of anesthesia more delicate and causing operations to be performed through layers of fat. It increases the probability of hepatic disease whenever it causes actual fatty infiltration of the liver. Increased mortality from accidents can be attributed to the fact that the obese person is a larger, clumsier and slower target as well as a poorer surgical risk after the accident.

On the other hand, it is likely that in many cases the relationship between obesity and disease is associative as well as causative. Table 1 indicates that while most correlations between causes of death and obesity are positive there are two causes of death which are negatively correlated with obesity: suicide and tuberculosis. In fact, it has been shown that the lesser mortality from tuberculosis in obese patients is not an artifact due to the decreased food intake of patients with a prolonged infection. Long-term studies[2] have shown that overweight persons are less prone to have tuberculosis. Incidentally, the decreased incidence of tuberculosis in overweight persons may explain why stoutness was so long equated with health in the Western world. (This is still the popular view in many underdeveloped countries.) Similarly, a causative relationship obviously is ruled out for the association of overweight with a decreased mortality from suicide. Apparently, the physical and psychologic characteristics which favor the development of obesity do not favor the development of the suicidal state.

Nonketotic diabetes in middle-aged obese patients is an illustration of the complexity of the association of obesity and disease. This syndrome probably entails associative factors (both hyperphagia and diabetes may result from the basic impairment in metabolism of carbohydrate) as well as causative factors. The "lipoplethoric" state of adipose tissue undoubtedly contributes to the deterioration of the glucose tolerance, which is generally improved by weight reduction. The relationship of obesity to heart disease may well be even more complicated. By exerting pressure on the capillaries, excess fat may cause increased peripheral resistance to flow; it may impair the function of the heart, because the heart itself is infiltrated with fat; and it may increase the work of an inefficient cardiovascular system because of the extra weight to be moved. Obesity and deficient cardiovascular function both may result from a sedentary, sluggish mode of life and from excessive consumption of an atherogenic diet.

It also is likely that the relationship between obesity proper, i.e., excessive adiposity, and disease has been obscured by the fact that the insurance tables which provide the bulk of available data were established in terms of body *weight*, not body *fat*. Selected "overweight" groups, such as the California longshoremen studied by Buechley, Drake and Breslow,[3] have a favorable health picture. In spite of these complexities, it is reasonable to conclude that the relationship of obesity and disease is sufficiently close to allow obesity to be considered a serious menace to health. Within certain limits, which I shall try to define, the known facts justify vigorous efforts to try to bring most patients to a reasonable weight.

Definition of Obesity: Limitations of Height-Weight Tables

It already has been implied that we are principally concerned with obesity, i.e., excess fat accumulation. Such a definition denotes a weight in excess of some norm for the

TABLE 1

ACTUAL AND EXPECTED DEATHS OF OVERWEIGHT MEN AND WOMEN BETWEEN 25 AND 74 YEARS OF AGE*

CAUSE OF DEATH	MEN		WOMEN	
	Deaths	*Expected deaths (per cent)*	*Deaths*	*Expected deaths (per cent)*
Principal cardiovascular-renal diseases	1,867	*149*	1,103	*177*
Organic heart disease, diseases of the coronary arteries, and angina pectoris	1,377	*142*	697	*175*
Organic heart disease	748	†	515	†
Coronary disease and angina pectoris	629	†	182	†
Cerebral hemorrhage	247	*159*	226	*162*
Chronic nephritis	243	*191*	180	*212*
Cancer, all forms	395	97	476	100
Stomach	62	85	34	86
Liver and gallbladder	33	*168*	46	211
Peritoneum, intestines and rectum	103	115	93	104
Pancreas	19	93	21	149
Respiratory organs	39	78‡	—	—
Breast	—	—	81	*69*
Genital organs	—	—	132	107
Uterus	—	—	103	121
Leukemia and Hodgkin's disease	26	100	23	110
Diabetes	205	*383*	235	*372*
Tuberculosis, all forms	24	*21*	20	*35*
Pneumonia, all forms	98	102	78	129
Cirrhosis of the liver	96	*249*	32	147
Appendicitis	76	*223*	41	*195*
Hernia and intestinal obstruction	39	*154*‡	31	*141*‡
Biliary calculi and other gallbladder diseases	32	152‡	30	*188*‡
Biliary calculi	19	*206*	50	*284*
Ulcer of stomach and duodenum	30	*67*	—	—
Puerperal conditions	—	—	43	*162*
Suicide	63	*78*	23	*73*
Accidents, total	177	111	74	*135*
Automobile	76	*131*	27	120
Falls	32	131	—	—

*According to estimates of contemporary mortality experience on standard risks. From 1925 to 1934 issues of the *Statistical Bulletin, Metropolitan Life Insurance Company*, ordinary department; traced to policy anniversary in 1950. Numbers in italics indicate statistically significant deviations from experience on standard risks.

†Satisfactory basis for comparison not available.

‡Based on mortality of standard risks from 1935 to 1939.

height, usually that established on the basis of the weight of insurance policyholders less than 30 years of age. Tables of "normal," "standard," "ideal" and "desirable" weights are widely available. In theory they make the diagnosis of obesity easy. If a patient weighs in excess of the normal weight for his height, he is overweight; if he weighs less, he is underweight. Actually, there are a number of reasons why the thoughtful physician will not be satisfied to substitute a table for clinical judgment.

The first tables of normal or standard weights in general use in the United States were compiled by Charles B. Davenport for the Medico-Actuarial survey of 1912. Heights of subjects were recorded with their shoes on, weights with their clothes on (1885 to 1900 clothes at that). So many of the weights ended in 0 and 5 that some observers concluded that the weights were estimated, not measured. There is even greater uncertainty when the phrase "with shoes on" is applied to women. The weight of women's street clothes also must have varied more from year to year in that era, which saw rapid changes in women's fashion.

The basis of these older tables is also vitiated by the fact that at the end of the nineteenth century the practice of buying life insurance was not as widespread as it is now. It was confined to a relatively small group of prosperous persons. Thus, the normal weight for a given age was normal for only a wealthy and relatively inactive group. This limitation was only partly corrected by the later life insurance company tables, which are based on the following modifications of the 1912 figures. The weights for men are predicated on their standard weight at age 30. This is based on the generally justified assumption that any increase in weight from then on is essentially adipose tissue. It may have been that the 1912 figures represented the weight of subjects after several years of inactivity, which would have caused all weights to be higher than they would have been at, say, age 25.

Corrections were made in the 1912 tables, because it was felt that those figures tended to overestimate the correct body weight of tall subjects and to underestimate that of short persons. Further adjustments were made to correct the gradation of values at successive heights. Then, groups were set up on both sides of the figures thus obtained. The three columns thus arbitrarily achieved were designated as ideal or desirable weights for persons with small, medium or large frames.

It must be noted that the weights for the various frames were never based on actual measurements of persons classified by frame. No method was given to determine the size of the frame, nor, for that matter, was the term defined. To be sure, the experienced physician may have acquired an implicit concept of frame based on skeletal size, as estimated by the size of the wrist and the ankle, width of the shoulders, etc. This concept is difficult to apply and certainly open to differing interpretations. Patients tend to give themselves the benefit of the doubt by "adopting" a large frame.

Obviously, if fatness is the problem, a definition based on fatness is necessary. While tables based on height-weight ratios may be useful for actuarial predictions or for public health studies on populations, they do not give the information the clinician needs in order to work with individual patients.

Measurement of Body Fat

About half the total body fat is deposited in the subcutaneous adipose tissue and is readily accessible for observation and measurement. Cursory visual examination of the naked subject generally will tell an experienced physician whether or not the patient is obese. The time-honored method of pinching the patient in appropriate places can settle doubt in many cases in which observation alone is inconclusive. While to date the caliper has been more an instrument of research than a tool of the general practitioner, its use is simple and permits actual measurement of subcutaneous fat thickness. Thus, the qualitative indication of manual pinching can be put on a systematic basis and validated by comparison with other methods. The true skin is only about 1 mm. thick, so that most of the variation in thickness of skin folds pinched up in different patients represents

differences in subcutaneous fat. Thickness of fat layers at many points on the surface of the body has been found to be closely correlated to the total fat content. Two locations are particularly informative and easy to reach. The first is the area over the triceps muscle on the back of the upper arm, midway between the elbow and the tip of the shoulder. In adult men, the thickness of the skin fold at this point varies from about 4 to 50 mm. or more. The next most useful site to test is over the tip of the scapula on the back. Other places for measurement include over the pectoral muscle on the chest, over the biceps, and various points on the abdomen.

As is well known, there are differences in localization of subcutaneous fat between children and adults. Small children have more fat on the arms than on the abdomen; adults show the opposite picture. There are classic differences in fat distribution between men and women. For instance, the thickness of fat layers on the calf of the leg is better correlated with total body fat in women than in men. Incidentally, this area is difficult to use for skinfold measurements, because the subcutaneous layer tends to be more tightly adherent, and it may be difficult to obtain a real skin fold.

Data obtained with calipers* of standard dimensions, which exert standardized pressure (usually 10 gm. per square millimeter of caliper jawface in contact with the skin), have been successfully compared with measurements obtained from roentgenograms of soft tissue. In turn, these determinations of subcutaneous fat have been correlated with calculations of total body fat obtained by densimetry. This method, based on weighing the subject first in air and then under water (with elaborate corrections for the air in the lungs and respiratory passages at the moment of weighing), was pioneered by Behnke and further refined by Keys and Brozek.[4] Total body fat can also be estimated from weight and total body water, which is obtained by heavy water dilution.

These methods have made it possible to demonstrate the differences in fat content between the sexes, between age groups, and between sedentary workers and those employed more strenuously, as well as to differentiate between overweight and obesity. It has been shown, for example, that the total body fat content of 25 year old women is at least 50 per cent greater than that of men of the same age. Thin, 40 year old women may have up to twice as much fat as muscular men of the same age. A picturesque determination conducted by Welham and Behnke[5] exemplified the distinction between overweight and obesity. The average guard or tackle on a college or professional football team weighs 200 lb. or more. Even in relation to his height and even when he is considered in the "large frame" class, the 6 ft., 200 lb. lineman is at least 10 per cent overweight, according to the best-known table of ideal weights. Yet, when navy scientists examined 17 professional football players, several of whom were former All-Americans, they found them endowed with a greater than normal specific gravity, indicating an abnormally low fat content. These overweight men were underfat. Conversely, it has been repeatedly shown, particularly by Keys and Brozek, that sedentary men of normal weight may, in fact, be obese in terms of being excessively fat.

Aging in the adult is particularly interesting. The old tables of normal height and weight appeared to condone the progressive accumulation of weight during maturity. This adjustment for age is one criticizable feature which has been eliminated in more recent tables. Data obtained by calipers and by densimetry clearly show that weight which accumulates after completion of muscular and skeletal growth is useless or dangerous fat.

Even if the same weight is maintained throughout adult life, active tissue is progressively replaced by fat. Keys[6] compared 33 younger (age 22 to 29) men with 33 older (age 48 to 57) men of the same height and weight. The fat content of the older men was found to be 50 per cent greater than that of the younger men (38 per cent at mean age 56, and 25 per cent at mean age 24). Active persons who continue to exercise into middle age

*Harpenden skin-fold calipers are available from British Indicators, Ltd., Sutton Road, St. Albans, Herts, England.

maintain a proportionately greater lean body mass than do sedentary people, but even in these subjects there is, if weight remains constant, a steady increase in total body fat. It would appear that the only way by which all patients (particularly highly muscular persons who stop intensive exercising) can prevent the progressive accumulation of fat is to stop gaining weight at the age of 25 and, over the later years, slowly to lose weight. In other words, patients should be encouraged to do what the French clinicians call *vieillir sec*—"to age dry."

The distinction between overweight and obesity and the variations in body composition with age pose some interesting problems of medical statistics. Is the 6 ft., 200 lb. overweight athlete really in the same risk category as the sedentary overfat person of the same height and weight? Is it as bad from the viewpoint of prognosis to carry too much muscle as it is to carry too much fat? Or, if disease were correlated with fatness rather than with weight, would the correlation between obesity and increased morbidity and mortality be even more striking? Certainly, the improvement due to losing weight (in this case, weight must be synonymous with fat) would suggest that the latter hypothesis is the correct one; however, the final proof of this theory has yet to be given.

The way in which a patient is obese may be important. Certain European clinicians attach considerable importance to the distribution of excess fat. Android obesity (the "John Bull" type) is characterized by accumulation of excess visible fat in the upper half of the body, and gynecoid obesity affects the lower half. Vague and associates[7] distinguished five categories of obesity, from hyperandroid to hypergynecoid, and considered that hypertension and diabetes occur much more frequently in the android than in the gynecoid type. Whether or not statistical evidence confirms this finding, Vague's studies testify to an analytic view of the relationship of obesity to disease which is likely to be more fruitful in defining types of syndromes than is classifying of weight according to universal standards which are doubtful.

Practical Criteria of Diagnosis and Final Targets of Treatment

A practical definition of obesity can be evolved from this general approach: A man may be described as definitely obese if his total fat content exceeds 25 to 30 per cent of total body weight; a woman, if her total fat content is in excess of 30 to 35 per cent.

Obviously, no elaborate measurements are needed to diagnose obesity in a man of ordinary height who weighs 250 lb. or in a woman who weighs 200 lb. On the other hand, clinical observation—looking at the nude body or pinching up skin folds—is necessary to diagnose obesity in a patient who is 10 to 30 per cent overweight according to standard height-weight tables. The use of skin-fold calipers, while not necessary for diagnosis, may allow obesity to be classified on a more quantitative basis. Obesity can thus be redefined on the basis of skin-fold thickness. Obesity is present in men if the skin-fold thickness over the triceps is greater than 15 mm. An exception may be made for very tall men (6 ft., 2 in. or more), in whom 18 to 20 mm. can be taken as the lower limit of obesity. Similarly, obesity is present in women if the skin-fold thickness over the triceps is greater than 25 mm. As a practical guide for the patient, male patients may be told that they should be unable to pinch a skin fold more than 1 in. thick on the abdomen under the navel; female patients should be unable to pinch more than 1.5 in.

A patient's desirable weight should be determined by his physician, not from an automatic reading in a table. Such a judgment should be based on the patient's appearance, his age, the natural history of his obesity, and information on his ancestry. It is often useful to know whether the obese patient resembles an obese parent or grandparent and to know the weight, duration of life, and cause of death of the latter. In a middle-aged man, the best target for weight reduction is often his weight at age 25; in a middle-aged woman, it is her weight at age 21 or 22. Weight accumulated after that time is excess fat, except, perhaps, in extraordinary cases in which muscle development has been pursued since that age. Set-

ting these weights as goals avoids questions about body build and gives the patient a sense of identification with the aim of the reduction program.

The physician may want to keep a youngster's weight near constant and to let the patient grow to the height considered approximate for the weight. Indeed, the role of the physician may be to convince his young patients, particularly adolescent girls, that they should increase their weight to what he regards as reasonable. There is little doubt that a proportion of the anemias, amenorrheas, etc. seen in adolescent girls results from self-inflicted malnutrition based on a wish to be thinner than is desirable for their health and, more often than not, for their appearance. The use of high-protein, high-mineral, high-vitamin, calorically restricted diets may permit pregnant women not to reduce their weight as such, but to maintain a constant weight during pregnancy and let delivery and postpartum weight losses effect the desired weight. Again, this desired weight should be determined by the physician, not by a mechanically applied and easily misinterpreted table or by the dictates of fashion.

The use of anthropometric data—skin-fold thickness, waist circumference, size of clothes, etc.—will bring home to the patient the point which she or, more particularly, he may not have been willing to face; namely, that he is not just "stout" or "heavy," but *fat*. The use of skin-fold or body measurements may thus help to motivate the patient. Determination of body fat is particularly interesting in situations in which muscle development and resultant protein weight gain are desired at the same time as is loss of fat, such as in inactive adolescents who should be reduced, at least in part, by increase in physical exercise.

Finally, only the application of systematic observation will allow "typing" of obese patients, a prerequisite for describing the various syndromes entailing obesity and a help in organizing clinical data. More important, the anthropometric, metabolic and psychologic identification of such types is a necessary step if the chances of success and effectiveness of treatment are to improve.

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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service

Case Report

A 29 year old white man was transferred to Hines Veterans Administration Hospital November 25, 1957, after six weeks' hospitalization elsewhere for heart trouble. One week prior to admission to the first hospital he had noted shortness of breath, weakness, anorexia, fever and pain in the left side of the chest. The episodes of pain would last for about 10 minutes at times, and they were not related to exertion. The patient believed that he had influenza. He consulted a private physician, who digitalized him. When his condition did not improve, he was admitted to the first hospital, where he was treated with digitalis, antibiotics and sedatives and oxygen when necessary. During this period the patient had an intermittent spiking fever, and he continued to be dyspneic; he was placed in an oxygen tent several times. Because he was unable to ingest food, he was given fluids intravenously. Four weeks before being admitted to Hines, he had a generalized skin eruption, which was attributed to penicillin. The eruption subsided in a few days, and, subsequently, swelling developed in his legs and abdomen. The swelling persisted until the present admission.

The patient's occupation was that of a clerical worker. He had had diphtheria and scarlet fever simultaneously when he was two years old and had had malaria in 1951. He had been in Korea from 1949 to 1950. He said that he had drunk five bottles of beer per day for the past seven years. A history of disease of the pulmonary system revealed that the patient had coughed up specks of blood two weeks before admission to this hospital. His father died of coronary thrombosis. The history was otherwise noncontributory.

Physical examination at the time of admission revealed that the patient was acutely ill, orthopneic, cyanotic and somewhat stuporous and apathetic. The neck veins were moderately distended. He weighed 175 lb., his temperature was 99° F., pulse 90, blood pressure 86/54, and respirations 28. Funduscopic examination showed slight narrowing of the arteries. There were moist rales over both bases and decreased breath sounds, with dullness over the right lower lobe. Bilateral expansion of the chest was equal. The border of the left side of the heart was 1 cm. to the left of the midclavicular line; the apex beat was not palpable. A gallop rhythm or split second sound was heard. The P_2 sound was noticeably accentuated and was louder than the A_2 sound. Regular sinus rhythm was present. The patient had marked edema of the abdominal wall, which made it difficult to palpate the abdominal contents. There was 4 plus pitting edema of the lower extremities, and the nail beds were cyanotic. Physical examination was otherwise negative.

Laboratory data—An x-ray of the chest on November 25 was reported to have been taken

TABLE 1

LABORATORY DATA*

TESTS	RESULTS FROM OTHER HOSPITAL					RESULTS AT HINES
	10/5	10/14	10/28	11/4	11/12	11/26
Red blood cell count	5.07	5.11	4.90	5.09	4.81	4.20
Hemoglobin (grams)	14.4	14.8	13.6	14.0	14.6	13.0
Hematocrit		46	40	39		43
White blood cell count	7000	5200	9800	16,400	19,500	9500
Neutrophils	53	75 (6)	81 (1)	74 (2)	83 (4)	83
Lymphocytes	43	16	18	23	11	7
Monocytes	1	3		1		8
Eosinophils	1				2	2
Basophils	2					
Sedimentation rate		2	38	26		
A-G ratio (gm. per cent)					2.73-1.95	
Nonprotein nitrogen					42	40
Sodium						133
Chlorine						88
Bicarbonate radical						22
Potassium						5.2
Glucose						88
Urine						
pH					Acid	Acid
Specific gravity					1.017	1.010
Albumin					Neg.	Neg.
Sediment					Neg.	Few red blood cells, granular casts, bacteria
Malarial parasites (1 smear)		Neg.				
Typhoid, *Brucella* and heterophil agglutinations			Nonreactive			
Serology			Nonreactive			
C-reactive protein						Strongly positive

*Serum transaminase on December 4 was 72 units.

in midexpiration, which made it difficult to evaluate the cardiac diameter. Bilateral hilar congestion was present, and the prominence of vascular shadows extended into the peripheral lung fields. The trachea was in the midline. The apical regions appeared to be normal. Blunting of the left phrenicocostal sinus had the appearance of pleural effusion or thickening at the left base. These findings were thought to indicate pulmonary congestion and edema, with pleural effusion of the left base.

An electrocardiogram taken by a private physician on October 5 had been interpreted as follows: "heart rate 125, sinus rhythm, abnormal tracing—suspicious of pericarditis or some metabolic disturbance or infection." On November 26, an electrocardiogram taken at Hines was interpreted as abnormal, showing sinus tachycardia, first-degree auriculoventricular block, low voltage, a possibility of an old anterior infarction, ST-T wave changes, and coronary insufficiency. Further laboratory data are summarized in table 1.

Hospital course—The patient was placed on a 2 gm. sodium diet and given digitoxin, ammonium chloride and mercurial diuretics. Several times during the following week, he complained of chest pain, which he believed was caused by a "machine," not by his heart. On November 29, the patient's temperature was 101° F. rectally; until that time it had been between 99 and 100° F. He was given tetracycline and prednisone. On December 2, the administration of potassium chloride was begun. Despite the therapy, there was no significant alteration in the edema, dyspnea, cyanosis or in the recurrence of chest pain. The patient became more restless and then stupor-

ous. He was placed in an oxygen tent, but he became progressively worse and died on December 4.

The findings were cardiomegaly, bilateral pulmonary congestion, and a slight pleural reaction at the left base.

Discussion

The three members of the medical staff who participated in this clinicopathologic conference presented their findings without prior knowledge of what the other discussants had said about this case.

DR. R. C. FRUIN (section chief of gastroenterology): After I had read the protocol of this case, I reviewed the cardiac findings for mention of a murmur. There was no indication of whether or not a murmur had been found. A further check revealed that no notation of the presence of a murmur had been entered on the patient's chart; therefore, it is assumed that none was heard.

This 29 year old man, apparently without previous history or symptoms, went into rapidly progressive and intractable cardiac failure. When this occurs in a man of this age, it is not ordinarily due to any of the common causes of cardiac failure; however, we cannot exclude the possibility of coronary arteriosclerosis in this case, especially since the patient's father died of coronary thrombosis. There is no previous history of rheumatic fever, and the patient's course would have been unusual for rheumatic fever or for subacute bacterial endocarditis complicating a rheumatic valvular lesion.

Most congenital cardiac anomalies become manifest before the person is 29 years old. However, it is not illogical in this case to consider a rupture of the sinus aortae, which is frequently congenital in origin but which can be due to syphilitic aortitis or to subacute bacterial endocarditis. With a rupture of the sinus aortae, there usually is a fistulous tract between the right sinus aortae and either the right ventricle or the pulmonary artery; occasionally, there may be a fistulous tract from the posterior sinus aortae to the right atrium. However, the fact that no murmurs were heard virtually eliminates such a diagnosis in this patient. Rupture of the sinus aortae almost invariably produces a rather profound and usually harsh murmur. Frequently, it sounds like the murmur of the ductus arteriosus, and it gives similar findings. However, the murmur of a ruptured sinus aortae usually is a little lower and a little to the right of that of the ductus arteriosus. Furthermore, a thrill is usually palpable, since the murmur of a ruptured sinus aortae is somewhat of a machinery murmur which is heard during both systole and diastole, but louder in the former. This ordinarily involves sudden and unremitting failure. This patient had failure of the right ventricle, with an increased P_2 sound. This condition usually can be diagnosed by angiocardiography, and, occasionally, it has been surgically repaired.

The possibility of an old myocardial infarction of an anterior wall, shown on the electrocardiogram taken at this hospital, also bears investigation. Although the infarction itself would not fit the course of this patient's illness, complications of the myocardial infarction, such as rupture of the interventricular septum, could conceivably have been present. However, in this condition also, there would be a loud, usually harsh murmur and progressive unremitting cardiac failure. In addition, rupture in the interventricular septum generally involves a very large area of infarction in the heart, which hardly would be questionable on an electrocardiogram. Thus, we can fairly well eliminate this as a possible diagnosis.

Rupture of a papillary muscle also is frequently due to myocardial infarction. It generally occurs in the posterior region; however, there could be a small anterior myocardial infarction, with rupture, involving the anterior papillary muscle. Such a rupture does not *always* produce a murmur; thus, this diagnosis could be considered a little more seriously. Rupture of the papillary muscle may be caused by trauma or by subacute bacterial endocarditis; however, it usually is due to myocardial infarction.

We also should consider the possibility of a cardiac tumor. Most tumors of the heart are secondary or metastatic tumors, and they frequently do not give rise to symptoms. The pri-

mary tumor ordinarily receives attention before the cardiac metastases are considered or produce symptoms. Kaposi's sarcoma involving the right atrium, the site at which it occurs most often, particularly seems to fit the course of the disease in this patient. Although the protocol does not mention enlargement of the right atrium in particular, the chest film showed a rather sharply outlined bulge, which is consistent with this diagnosis. The fact that the patient believed he had influenza at the onset of symptoms also is indicative of Kaposi's sarcoma of the right atrium, which often is heralded by an influenzalike episode. Patients experience weakness, profound malaise and fever. A bulge on the right atrium usually will be noted, although this is not an essential finding. Of course, many other tumors may involve the heart, but most of them would not give this course. For example, a myxoma can involve the right atrium, although it most often involves the left atrium. A myxoma may give a ball-valve type of action, with attacks of cyanosis, profound syncope, etc. Sarcoma of the myocardium may be considered as another possibility; this is quite rare and can simulate or be confused with insufficiency of the myocardium associated with failure.

I originally thought that this patient's condition indicated a rupture of the sinus aortae; however, the absence of a murmur eliminated this diagnosis. Therefore, I have decided on a diagnosis of Kaposi's sarcoma, with rupture of the anterior papillary muscle.

DR. E. J. HERTKO (resident, general medical service): The protocol of this case seemed to indicate that this was a fulminant course of heart disease in a relatively young man who previously had manifested practically no cardiac symptoms. At the time the patient died, the heart was not greatly enlarged; with the exception of low blood pressure, other cardiac symptoms were not very severe. The pulse rate of 90 was not remarkable. I considered five possible diagnoses: (1) pericarditis, (2) an acute fulminant course of coronary arteriosclerosis, (3) aortic stenosis, (4) myocarditis, and (5) an adult form of endocardial fibroelastosis.

There really were no dramatic findings in the laboratory data of this case. Although the C-reactive protein was 4 plus, this is a nonspecific test and indicates only that the patient did have some inflammation. The slight elevation of serum transaminase was not remarkable, and this can be caused by damage to cardiac or skeletal muscle or to the brain, liver or kidney.

The patient did have some electrocardiographic changes which would be compatible with pericarditis; however, the x-ray did not demonstrate any findings related to pericarditis. I also believe the fulminant course of the patient's illness rules out this diagnosis.

I considered the possibility of aortic stenosis because the patient had no murmur. In addition persons may live with this condition for many years and then die very suddenly, and this man died only eight weeks after the onset of symptoms. However, he had no other symptoms of aortic stenosis. If this condition had been present, some hypertrophy of the left ventricle probably would have been found, but this could not be demonstrated.

Many of this patient's symptoms, especially the severe weakness, anorexia, weight loss and precordial pain, would be compatible with a diagnosis of myocarditis. A low fever and a slight cardiac enlargement are usually present in myocarditis, although the cardiac size may be normal. Frequently, there may be no auscultatory changes in the heart sound. The gallop rhythm and duplication of the second sound in this patient were consistent with myocarditis. Other symptoms and the electrocardiographic changes also were compatible with this diagnosis.

If this diagnosis is to be considered seriously, we must ask what caused myocarditis in this patient. The diseases which produce myocarditis are too numerous to mention. The scarlet fever and diphtheria which this patient had during childhood conceivably could have caused myocarditis; however, I do not believe that these diseases were responsible for his last illness. Viral infections also may cause myocarditis. This patient became ill during an influenza epidemic in October 1957. Although influenza has been known to cause myocarditis, some authors state that this is unusual and

that myocarditis ordinarily occurs only in complicated cases. This patient's course also was consistent with Fiedler's myocarditis, which sometimes is called primary idiopathic pernicious myocarditis. The prognosis ordinarily is fatal, and, in spite of treatment, these cases usually run a fast downhill course. The onset of this type of myocarditis is usually abrupt. Fever, chills, lassitude, anxiety and electrocardiographic changes of the type found in this patient are further indications of this condition. The cardiac sounds ordinarily are not altered, and a gallop rhythm is frequently present. All these signs seem to indicate a diagnosis of myocarditis in this patient.

Reviewing the literature on myocarditis, I found that in 1941 Saphir stated that isolated myocarditis often causes rapidly progressive myocardial failure or sudden death. Another investigator found that influenza frequently causes myocardial damage, and that it may be the first or only indication of the disease; however, it most commonly appears in the convalescent stage. A general review of the literature, particularly of the writings of Gore, Saphir and Lichtenberg, which appeared between 1947 and 1957 showed that practically every case of myocarditis cited was first manifested by cyanosis, dyspnea, orthopnea and hypotension. All these findings seem to substantiate the diagnosis of myocarditis in this patient.

I also considered the diagnosis of adult endocardial fibroelastosis. Within the last several years, perhaps a dozen or so cases of this disease have appeared in the literature. It is most commonly found in infants, and in about 90 per cent of cases it causes death within the first year of life. However, in the last 10 or 15 years, it has been found that persons with this condition have been living longer. The disease has been diagnosed in persons of 15, 20 and 24 years of age. Postmortem examinations have shown changes which are compatible with the fibroelastosis found in infants.

Another entity recently has been reported which is almost the same as the fibroelastosis of infants but which differs in some aspects, especially in the location of the pathologic changes in the endocardium. Different names have been given this disease. One author called it endocardial fibrosis. Several years ago articles were written about a rapidly fulminant type of heart disease found in West African soldiers; this was called endomyocardial fibrosis. In the April 1957 issue of the *British Heart Journal,* some cases were discussed in which there was a diffuse thickening of the mural endocardium of one or both ventricles and fibrosis of the myocardium, confined largely to the ventricular wall. The coronary arteries in these patients were essentially normal. This condition was called diffuse endomyocardial sclerosis.

Certain findings in this patient are compatible with this diagnosis. The disease usually occurs during the third or fourth decade of life; this man was in the third. Ordinarily, there are no relevant findings in the family history, and this patient's family history seems essentially negative except for the fact that his father had a coronary thrombosis, which is not extraordinary. The disease usually is not found in siblings. This type of heart-failure generally occurs on the right or left side. In addition, patients may have this condition for a number of years and then suddenly go into heart-failure. The failure is believed due to the fact that the endocardium is so rigid that it interferes with the ventricular diastolic filling and the systolic expulsion of the blood. Many endomural thrombi and embolic phenomena also may be present in this disease.

The size of this patient's heart, which was not immensely dilated (as in a valvular-type heart disease), and the fulminant course of the disease almost mimic a type of constrictive pericarditis. The disease which I have just described resembles this condition. Thus, my diagnosis in this case would be adult endomyocardial sclerosis.

DR. W. J. DONNELY (section chief of hematology and metabolism): This 29 year old man had a most unusual and precipitous downhill course and died two months after the onset of congestive heart-failure. In addition to showing all the signs of congestive heart-failure of both the right and left sides, his illness was characterized by fever, marked debility, precordial pain, hemoptysis and a peculiar

failure to respond to the usual cardiac therapeutic measures as well as to antibiotics and a short course of steroid therapy. The usual significant omissions are noted in the protocol: the absence of the antistreptolysin-O titers, which would have been important in excluding an active rheumatic carditis; the absence of blood cultures in the presence of febrile heart disease; and the absence of adequate roentgenographic studies of the heart, which probably was due to the patient's condition. Other laboratory findings are not particularly helpful. Neither the positive C-reactive protein nor the slightly elevated serum transaminase is significant. The decreased serum albumin is an interesting finding, but it is a rather common one in edematous states and need not be considered here. The absence of proteinuria is most unusual; I have yet to see a patient in profound congestive heart-failure who does not have proteinuria.

The signs and symptoms of congestive heart-failure in this patient are of no value in elucidating the specific etiology of his condition. He surely had some cardiac enlargement; he had a sinus tachycardia and, quite remarkably, a very loud second pulmonic sound. As a sign of pulmonary hypertension in a febrile patient who has precordial pain and who has had hemoptysis, a loud second pulmonic sound surely indicates sustained multiple pulmonary emboli. No murmurs were noted. The gallop rhythm was simply a sign of congestive failure; it probably was a protodiastolic gallop. The first-degree heart block shown on the electrocardiogram and other nonspecific changes are not helpful in establishing diagnosis, since these changes may occur in a variety of cardiac diseases. The chest film confirmed the clinical opinion that the patient had marked failure of the left ventricle. Certainly there was some nonspecific enlargement of the heart. The chest film showed that the right cardiophrenic angle was still acute; thus, there was no evidence that the patient had a pericardial effusion.

In making an etiologic diagnosis in anyone with heart disease, we consider first the usual varieties: congenital, coronary-arteriosclerotic, hypertensive, rheumatic-valvular and syphilitic. The findings in this case do not point to any one of these. Morphologically, there is no direct evidence of either pericardial or endocardial involvement. However, there is a long list of myocardial conditions which conceivably could be considered. For the purposes of this discussion, I shall call them "myocardiopathies." These may be classified into two major groups, which are described as follows:

1. There are many types of myocarditis which are generally considered to represent true myocarditis; the most common are those associated with systemic infections, such as lobar pneumonia with a secondary septic myocarditis. The myocarditis of rheumatic fever also is in this group. It would seem incredible, however, to consider an active rheumatic carditis as the initial manifestation of a rheumatic process in a patient of this age in whom there was no evidence of prior valvular damage due to an occult rheumatic episode.

2. Myocarditis due to chemical agents and to hypersensitivity reactions to various substances has been described. Of this type only acute interstitial myocarditis, sometimes called Fiedler's myocarditis, seems a possible diagnosis in this patient. Fiedler's myocarditis almost always is a postmortem diagnosis. It is peculiar in that it does not involve the endocardium or pericardium, which accounts for its sometimes being called an isolated myocarditis. This diagnosis seems more probable when we realize that this disease is frequently seen in the third decade of life and occurs most commonly in men. Pathologically, it is characterized grossly by a dilated, hypertrophied heart and by many intramural thrombi. Clinically, patients with this disease have a rapidly progressive downhill course, with congestive failure; they also have fever, and the early course of the disease may suggest myocardial infarction. Dyspnea, weakness, cyanosis and all the symptoms exhibited by this patient are present. The disease also produces symptoms of both pulmonary and systemic embolization, since the mural thrombi occur in both sides of the heart.

There is a long list of myocardiopathies not generally considered inflammatory, including the clinicopathologic discussant's staunch

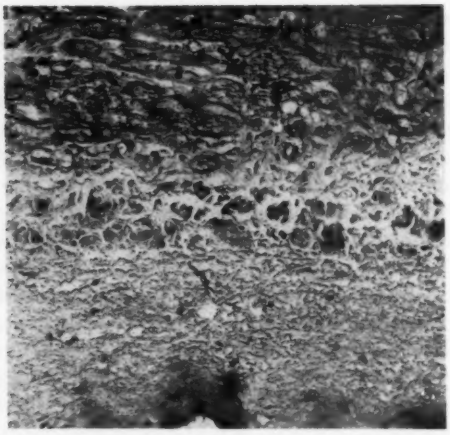

FIGURE 1. Photomicrograph showing loss of cardiac muscle fibers with replacement by fibrous tissue and collagenous material.

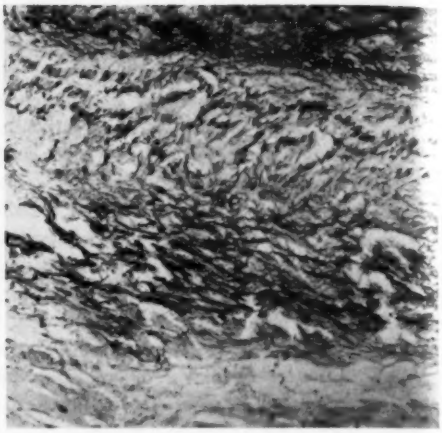

FIGURE 2. Photomicrograph of elastic tissue stain showing marked increase in elastic tissue.

stand-by, periarteritis nodosa, as well as scleroderma, amyloidosis, sarcoidosis, systemic lupus, etc.; however, there is no direct evidence of any of these in this patient, and I do not consider them as possible diagnoses. I have reserved for final consideration the diagnosis which I believe is the most likely one.

There are always several requirements for a clinicopathologic diagnosis: (1) The diagnosis cannot be and is not made clinically; (2) the process must be very interesting pathologically; and (3) the lesions must photograph well. Let us therefore consider endocardial fibroelastosis, a rather rare disorder which was found in only 20 cases in a review of 10,000 consecutive autopsies at a large general hospital. Almost half the patients in this series were children or infants. The age of onset of the disease in adult patients ranged from 16 to 71 years.

Endocardial fibroelastosis is characterized by a relatively localized or extensive fibroelastic thickening of the endocardium and the subendocardial areas. It is thought to be most probably of congenital origin; however, many investigators believe that the adult form of the disease is acquired. Since it is also characterized by rapidly progressive congestive failure and by the presence of mural thrombi which embolize into both lesser and greater circulations, I believe endocardial fibroelastosis was the cause of this patient's cardiac disease.

Postmortem Findings

DR. MYRON E. RUBNITZ (chief of pathology): The clinical description of this patient showed marked cyanosis; distention of the abdomen obviously indicated a large amount of ascites, and there was some pleural effusion on the right side. The heart weighed 410 gm. and was markedly dilated. There were no changes in the coronary arteries. Marked thickening of the left ventricular wall seemed to be localized along the posterior section. A large mural thrombus was found in the left auricular appendage, and there was a questionable clot in the right auricular appendage. The lungs showed multiple pulmonary infarcts measuring up to 3.5 cm. in diameter. The liver presented evidence of marked chronic congestion. The spleen showed an old infarct and was twice the normal size. The kidneys likewise showed questionable small infarcts.

Figure 1 shows actual loss of the cardiac muscle fibers, with replacement by fibrous tissue and thickened collagenous material—huge hypertrophic muscle fibers with bizarre-appearing nuclei. A partial section of a small blood vessel did not reveal any particular vascular disease.

From the clinical and microscopic findings in this case, a diagnosis of myocarditis, with etiology unknown, did not seem quite probable. The marked thickening of a section of the endocardium is not the usual finding in a case of myocarditis. In addition, the changes in the endocardium and the myocardium, without other evidence of, perhaps, rheumatic heart disease, were not compatible with this diagnosis. On the advice of some of the people who had seen the slides, an elastic tissue stain was done. Figure 2 shows a marked increase in elastic tissue in sections taken from the thickened endocardium. This is far more elastic tissue than would ordinarily be seen in a normal endocardium. This finding raised a doubt about the diagnosis of myocarditis. After examination of much of the literature, it became apparent that this was a case of adult fibroelastosis.

In view of the fact that up to 1956 only about 24 cases of fibroelastosis in adults had been reported in the literature, I think it is especially interesting that two of the discussants arrived at this diagnosis. Fibroelastosis has been reported in patients as young as 18 years of age and as old as 65 or 70, the average age being between 40 and 60. Low blood pressure, exhibited by this patient, also was reported in many of the cases described; in fact, one patient had a blood pressure of 90/60. The low voltage and bizarre T wave changes seen in the electrocardiogram also were seen in the cases described in the literature. Antemortem diagnosis was not made in any of the cases reported.

Valvular findings, particularly involving the mitral valve, were described in about 50 of the cases in the literature. There were no findings of this kind in this patient. The diagnosis rests on the increased elastic fibers found in the endocardium, which were shown by microscopic examination.

Coronary sclerosis occurs rarely and usually in older persons. There was nothing in this case to indicate arteriosclerosis. Myocardial fibrosis, which occasioned the diagnosis of myocarditis, is quite common and is seen in almost 90 per cent of the cases of adult fibroelastosis. The mural thrombi, source of the emboli, also are quite common and very often occur not only in the auricular appendages, as in this case, but also in the ventricles.

Theories of Etiology

There are some very interesting theories concerning the etiology of fibroelastosis. The ideas of Schaffer are markedly different from those of other investigators. His very long and interesting treatise seems to be based on the concept that an increase in the force exerted on the muscle, apparently from some obscure original dilatation of the heart, causes the formation of the elastic fibers. Lynch and Watt believe a primary condition in the myocardium leads to some type of intramural thrombus which then organizes and forms elastic fibers. Weinberg and Himmelfarb think that this is a developmental defect. This could very well be true in infants, but the cause of the defect in 60 or 70 year old patients is obscure. Weinberg and Himmelfarb's ideas concerning anoxia are probably the most pertinent, particularly since the young erythroid cells found in this condition apparently indicate definite evidence of some marked anoxia. Rosahn believes this disease is some form of generalized vasculitis. Although some changes in the small vessels were seen in this patient, they were obscure and evidently did not affect the etiology of the disease.

DR. EDWARD O. WILLOUGHBY (assistant chief of medical service): What was the difference between the thickness of the two ventricles?

DR. RUBNITZ: The left ventricle was about 1.8 cm., and the right ventricle was about 0.5 cm. They were definitely thickened.

DR. WILLOUGHBY: How did the area of thickening compare with the area of the entire heart?

DR. RUBNITZ: The area of thickening was small and not diffuse. It was found on the posterior wall and probably measured only about 3 or 4 cm. at the greatest diameter.

Editorials

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HEALTH FOR PEACE*

WRITING in *The New York Times Sunday Magazine* seven years ago, Arnold Toynbee said, "The twentieth century will be chiefly remembered . . . as an age in which human society dared to think of the welfare of the whole human race as a practicable objective."

One, and perhaps the most significant, feature of social development which gives hope of Mr. Toynbee's objective becoming reality is the increasing recognition throughout the world that the security and welfare of the human race are interdependent within each geographical area of the world and that the security and welfare of each geographical area of the world are dependent on the security and welfare of the world as a whole.

I, for one, and I am sure this concept is shared by the great majority of people in the world regardless of their race, religions, nationalities or professions, believe this growing recognition of mutual interdependence has not resulted solely from practical necessity. I believe it also represents our ability as our society matures to give fuller expression to a feeling that is as old as mankind itself—to the desire to share with and help one's neighbor.

It has long seemed to me that in the field of health and rehabilitation, we have a uniquely effective area of service and of responsibility for working toward international understanding. Health, including rehabilitation services for the handicapped, is fundamental to the prime democratic concept of equal opportunity for all. A world in which good health is enjoyed by but a few cannot be a politically stable world. How can the man who is doubled up by pain and disability stand up and fight militantly for the principles of democracy and freedom? Unless he can work and produce, how can he enjoy the fruits of his own labor and become a customer for the goods which all of the world wants to sell him? Unless he can produce and earn and then buy from the rest of the world, how can his standards of living be increased?

Good health is fundamental to economic self-sufficiency. Dr. Charles W. Mayo summed up this relationship aptly when he said with

*Abstract of remarks presented before the Brotherhood Week luncheon of the National Conference of Christians and Jews in New York.

great simplicity, "1. Sickness makes people poor. 2. Poverty makes people sick."

Today, the Senate and the House of Representatives of the United States have before them a proposal which could go far to break this chain described by Dr. Charles W. Mayo. I refer to the International Health and Medical Research Act of 1959 introduced in the Senate by Senator Lister Hill and in the House of Representatives by Representative John Fogarty.

This legislation, known popularly as the "Health for Peace" bill, would create within the National Institutes of Health a new National Institute of International Medical Research with an annual appropriation of $50,000,000. These funds would be used to encourage and support research and the exchange of information on research, the training of research personnel, and the improvement of research facilities throughout the world.

The bill would authorize grants to support such activities ranging from research in basic science to research in rehabilitation. Grants could be made to foreign and American universities and research organizations and to voluntary and governmental international agencies, e.g., the World Health Organization.

Under the plan, a National Advisory Council for International Medical Research, composed of nongovernmental leaders, would establish policies, make recommendations, and approve grants and loans under the program. The existing specialized advisory councils on heart, cancer, arthritis and metabolic diseases, neurologic diseases and blindness, vocational rehabilitation and similar specialized fields would advise the new National Advisory Council for International Medical Research on specific projects within their particular areas of interest and competence.

The program would not replace any of our current programs of multilateral international health activities through the World Health Organization or UNICEF or any of our bilateral activities conducted through the International Cooperation Administration. Nor would it supplant the research programs being conducted in the United States through the National Institutes of Health. It would enhance these activities and at the same time provide a mechanism and funds for uniting science throughout the world in a greatly expanded global attack on disease and disability.

The key factor in grants from the new National Institute for International Medical Research, over and above the criteria which are usually applied to research projects, would be their international implications.

Although there are innumerable corollary values in Senator Hill's proposal, it is based primarily on recognition of the fact that medical research is so highly complex and interrelated that victory over any disease or disability can be accomplished only through the research results of many scientists throughout the world.

A new *ad hoc* Committee on Health for Peace has been formed by many of our nation's leading scientists, clinicians, businessmen and civic leaders to increase the public understanding of the principles underlying increased United States support of international health work. Chairman of this new Committee on Health for Peace is General Omar Bradley, while Dr. Detlev Bronk, president of the Rockefeller Institute for Medical Research, is chairman of the Scientific Advisory Committee.

The Committee on Health for Peace will not engage in fund-raising activities; nor will it attempt to duplicate the important work of the National Citizens Committee for the World Health Organization. Its function will be solely to increase public understanding of the importance of international cooperation in health and medical research.

It is significant that when Senator Hill reintroduced the "Health for Peace" bill in the Senate, 59 of his colleagues in the Senate joined him in cosponsorship. I believe this proposal will have great public support not only among individuals and national organizations interested particularly in health but also among organizations which are dedicated to increasing world brotherhood by increasing world understanding.

The people of the United States have demonstrated, through their willingness to contribute both tax and voluntary funds, their

firm belief in the value of medical research. Most, I am confident, will also agree that while we and the rest of the world are spending billions of dollars for research for instruments of death and destruction in our struggle for survival, we should spend a few millions positively on promoting health, happiness and human understanding in our struggle for peace.

HOWARD A. RUSK

Professor and Chairman, Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center: President, World Rehabilitation Fund, and Chairman, American-Korean Foundation

THE NATURAL HISTORY OF HYDROCEPHALUS

OFTEN in philosophical works in the field of medicine, it is suggested that much more needs to be known about the natural history of a disease that is entirely untreated. For instance, data are available of what happened many generations ago in cases of syphilis, smallpox and leprosy which were untreated. Modern medicine does not, of course, sit idly by watching the progress of disease; yet, in certain conditions or under certain circumstances, a disease does go on to its conclusion with little or no attempt at treatment. This is true occasionally, but much more rarely now than in the past, of persons belonging to cults which do not believe in medical care.

An unusual article by Dr. K. M. Laurence,[1] a research fellow in hydrocephalus and spina bifida in the department of morbid anatomy of the Hospital for Sick Children, Great Ormond Street, London, describes what occurs when hydrocephalus arrests without surgical intervention. Dr. Laurence has followed the records of children less than 13 years of age who were seen in two different hospitals in Great Britain between January 1938 and December 1957. Altogether, he reported 57 patients with different types of hydrocephalus who received a variety of surgical procedures during the 20 years under consideration. The remaining 182 patients were not operated on. In 43 cases, the hydrocephalus was believed to have been caused by malformation, in 59 by trauma, in 42 by infection, in 4 by tumors and in 34 by unknown factors. All but three of these patients were traced, and those surviving were re-examined. Intelligence tests were carried out on those more than 18 months of age.

The disease usually began during the first six months of life, and was diagnosed by progressive head enlargement, raised intracranial tension and, often, depression of the optical axes. In a few instances in which hydrocephalus began later, the cause was meningitis. Most children who died of this disease did so within the first 18 months of life. The cause of death was usually cardiorespiratory arrest caused by progressive medullary failure. Eighty-one of the 182 children were alive and well with the hydrocephalus spontaneously arrested. In about one-half of the cases, the disease had arrested spontaneously. Eighty-nine patients had died. Many of the children had physical handicaps in addition to mental impairment. Those with spina bifida cystica were often severely paralyzed, especially in the legs and sphincters; the others had spasticity, joint contractures, incoordination or impaired vision, among other symptoms. Twenty-seven of the 81 children with arrested hydrocephalus did not have physical disability.

In previous reports, one investigator found 19 of 160 patients with spontaneous remission. Another investigator found 30 of 70 cases with spontaneous arrest. The fact appears that the worst cases of hydrocephalus are fatal in the first three months. The mildest forms sometimes are so mild that they are not reported. In view of the more hopeful prognosis suggested by these figures, Dr. Laurence believes that the reported results of surgery in hydrocephalus may have to be reassessed.

Such reports as this indicate the desirability of more extended studies in various diseases as to the natural history of the disease when untreated or when treated by conservative rather than radical methods.

MORRIS FISHBEIN

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MALARIA

THE eighth assembly of the World Health Organization took special action urging that malaria eradication take priority above other health measures among all nations. The assembly decided that the World Health Organization should take the initiative, providing technical advice and encouraging research and the coordination of resources in implementation of a program which would have as its ultimate objective the world-wide eradication of this disease. Such a program is clearly feasible, since many areas of the world already have eliminated malaria from places in which it was widespread. Those sections of the world that have adequate funds will need to aid less privileged areas in accomplishing this important objective.

Since the introduction of insecticides, which play a great part in eliminating malaria, many mosquitoes have developed increasing resistance to toxic substances. Thus, science and disease are again at war; the speed with which science acts may be the determining factor in winning this battle against the world's most prevalent disease.

As recently as 1955, malaria affected 200 million people and caused two million deaths per year. Conceivably, more than one billion people are at this time exposed to malaria. Where malaria prevails (in 120 of a total of some 200 countries and territories), the disease interferes with economic development. Quite certainly the eradication of malaria is better than spending the vast sums that are now spent on medical care, including drugs and hospitalization. Malaria injures manpower by causing unnecessary deaths at an early age, and the loss of working time among those affected by the disease is tremendous. The World Health Organization estimates that the average six day attack involves a loss of 130 million man-days annually in India, 40 million in Mexico, and from 9 to 9.5 million in Thailand. Great tracts of fertile land lie uncultivated in Asia, Central America and Africa because of malaria; indeed some of these areas have been completely abandoned. In Ceylon, India, Java and Mexico, much rich agricultural land that formerly was unused because of this disease is now under cultivation.

The malaria eradication campaign includes four phases: (1) A survey is made, plans prepared, and personnel recruited. (2) Over a period of three or four years every habitation is sprayed with insecticide twice a year. (3) Cases of the disease are detected and treated with antimalarial drugs. When a three year surveillance fails to reveal any new cases, the eradication is considered successful. (4) The campaign is maintained by checking for signs of recurrence and guarding against the introduction of new human reservoirs of infection.

It is estimated that during the next five years approximately $600 million will be required for malaria eradication. These funds are largely available from such sources as the United States International Cooperation Administration, the USA Loan Capital, and the United Nations Children's Fund. The World Health Organization will be responsible for $60 million; some will come from the regular budget, but approximately $50 million is to be raised from voluntary contributions.

MORRIS FISHBEIN

REFERENCE

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MORE AND MORE WIDOWS

THE Bureau of the Census estimates that in March 1958 there were 8,047,000 widows in the United States, which is an increase of more than one million widows since 1950 and is almost three times as many widows as there were in 1900. About one of every eight women more than 14 years of age is a widow. The Statistical Bulletin[1] of the Metropolitan Life Insurance Company notes, furthermore, that the majority of women who become widows still have many years of life before them. The life expectancy of women is much longer than that of men. One-fourth of all women at ages 55 to 64 are widowed; three times as high a proportion are widowed at ages 75 and over.

These statistics emphasize what everyone

who observes the passing scene may have suspected. In all the great residence hotels which are found in urban areas there are tables in dining rooms where six or more widows gather together to have their dinner. The majority of widows past 50 years of age are lonesome people. Frequently, young widows are forced to seek gainful employment even though they have young children requiring care. Unfortunately, many women who lose husbands late in life are handicapped by an inability to find employment because of age or because of lack of ability in any special field. The benefits provided by Social Security are minimal and hardly sufficient for their living.

The problems of our aging population are arousing more and more concern among socially minded thinkers. In a recent session, the House of Delegates of the American Medical Association proposed that physicians lower their charges for the aged and attempt to provide in other ways for meeting the medical needs of older people. Among the aged, the widows are a special sector whose social needs require more than ordinary consideration.

MORRIS FISHBEIN

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SELF-HELP DEVICES

EVERY person oriented both psychologically and medically to the physical problems that concern mankind is convinced that self-help is in itself an important therapeutic mechanism. The number of physically handicapped persons in the United States approximates more than 25 million at all times. Every year at least 400,000 more people join this group. If a person is able to accept his physical disability and adjust himself to it, he becomes thereby far more capable of total rehabilitation. The use of the self-help device is now recognized as a major factor in overcoming all types of physical disability. The time is not too far past when people refused to wear eyeglasses because of imaginary prejudices, and hearing aids are just now beginning to be generally accepted. For many centuries, however, people have used canes to support unstable locomotion.

In the Institute of Physical Medicine and Rehabilitation in New York City, a veritable museum of self-help devices is available for inspection by the interested person, and several manuals and books describing such devices are already available. However, the interest more recently aroused in this subject makes the development of self-help devices almost a monthly occurrence, and their widespread adoption is greatly to the interest not only of the handicapped person but also of his family and the community in which he lives.* Self-help devices are not necessarily prostheses but might well be incorporated into some of the prosthetic devices already available. In its simplest form, a wheel chair is a self-help device. A safety belt which enables a woman on crutches to fix herself with another safety belt so that she can stand and work safely is a self-help device. The list of such devices is fascinating. To observe them in action borders on witnessing the miraculous. And best of all is to observe the new feeling of confidence and successful performance which comes to the handicapped person helped in this way.

MORRIS FISHBEIN

*To provide current information in this field, POSTGRADUATE MEDICINE this month starts publication of a regular department on self-help devices and their applications. In this issue, the feature appears on pages 443 to 445.

rinase* in the management of diabetes:

nalysis of long-term experience in 9,168 patients

A little over a year ago, a new epoch began in the treatment of diabetes: Orinase became available for general clinical practice. Today, more than 400,000 diabetics are enjoying the advantages of oral management.

the mass analysis of 9,168 patients

What has experience taught us? In this comprehensive report you will find the results of a detailed analysis of 9,168 patients observed on Orinase therapy by 420 cooperating physicians and clinics for periods ranging up to more than twenty-eight months. Coded IBM cards were employed for mass analysis, and in addition each case report was reviewed for observations and laboratory data which could not be readily submitted to an IBM coding procedure.

the results

The evidence is impressive. In brief, these are the highlights of the mass study: While patients who developed diabetes at the age of 40 or later are the most likely candidates for Orinase therapy, diabetics with a 20 to 40 age-of-onset also deserve a careful trial with the drug. A favorable response to Orinase, moreover, can be anticipated in certain patients who chronologically might be classed as juvenile or growth-onset diabetics, but whose disease behaves like the stable, maturity-onset form.

It is well established that "Orinase-responsive" diabetics show more stable blood sugar levels and less glycosuria on Orinase than on insulin. It is also noteworthy that you can expect excellent or good control of diabetes with Orinase in many patients who show only a fair or poor response to insulin. Of great significance, too, is the fact that four times as many diabetic patients respond favorably to Orinase as do to dietary control alone.

The remarkable safety of Orinase was confirmed by this study of thousands of patients. In only 1.5% of cases did side effects require cessation of therapy, and in no case were serious toxic reactions observed.

the answers to many questions

On the following pages are presented the most pertinent findings of this study. These should serve as a useful guide in the use of Orinase in your own practice.

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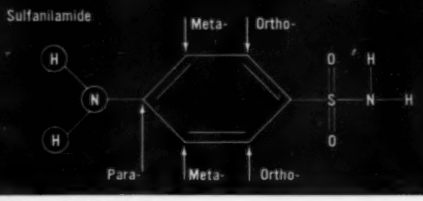
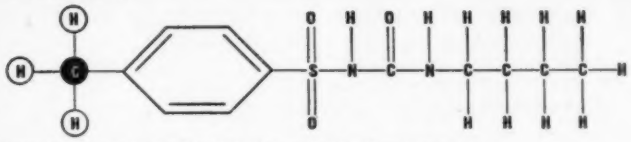
Front and back cover: the Orinase Case Study form used in the mass analysis of 9,168 diabetic patients.



Orinase (tolbutamide)



Orinase is not a sulfanilamide derivative or "sulfa" drug. The substitution of a methyl group for an amino group in the para position of the benzene ring of Orinase renders the compound bacteriostatically inert and devoid of goitrogenic effect. Orinase is free of the potentially serious toxic properties of sulfanilamide derivatives.

In which age groups has Orinase therapy proved successful?

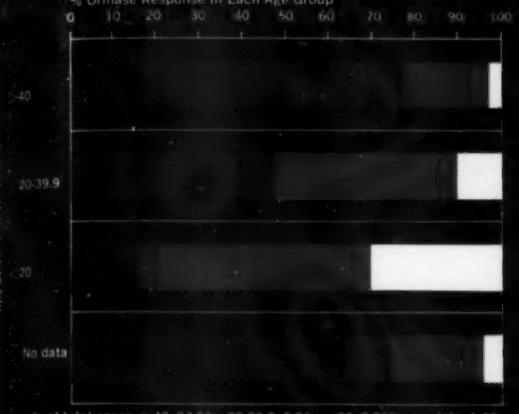
It is evident that the likelihood of a satisfactory response to Orinase therapy is greatest in patients whose diabetes developed after the age of 40. Nevertheless, at least 2 out of 5 diabetics who are diagnosed between the ages of 20 and 40 can achieve good to excellent control on Orinase.

The satisfactory responses in some patients whose diabetes became manifest before the age of 20 may be explained by the fact that these were patients whose disease, while chronologically juvenile or growth-onset diabetes, behaved like the stable, maturity-onset form.

How does body build affect Orinase response?

Body build does not seem to be a major determinant of response to Orinase therapy. While a somewhat lesser incidence of satisfactory control was found in those patients of asthenic body build, there was no difference in the incidence of excellent and good control between those of medium and obese physique.

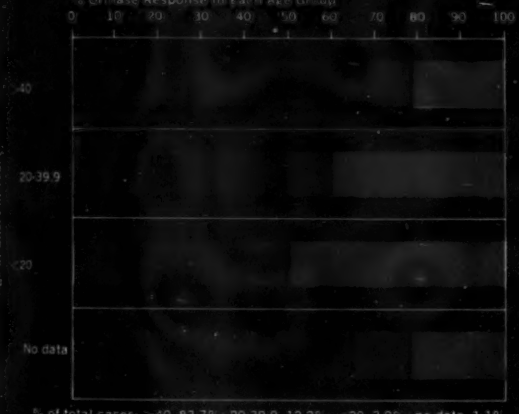
Table I. Age Distribution at Time of Treatment and Correlation with Orinase Response



% of total cases: >40, 92.5%; 20-39.9, 5.0%; <20, 0.96%; no data, 1.5%

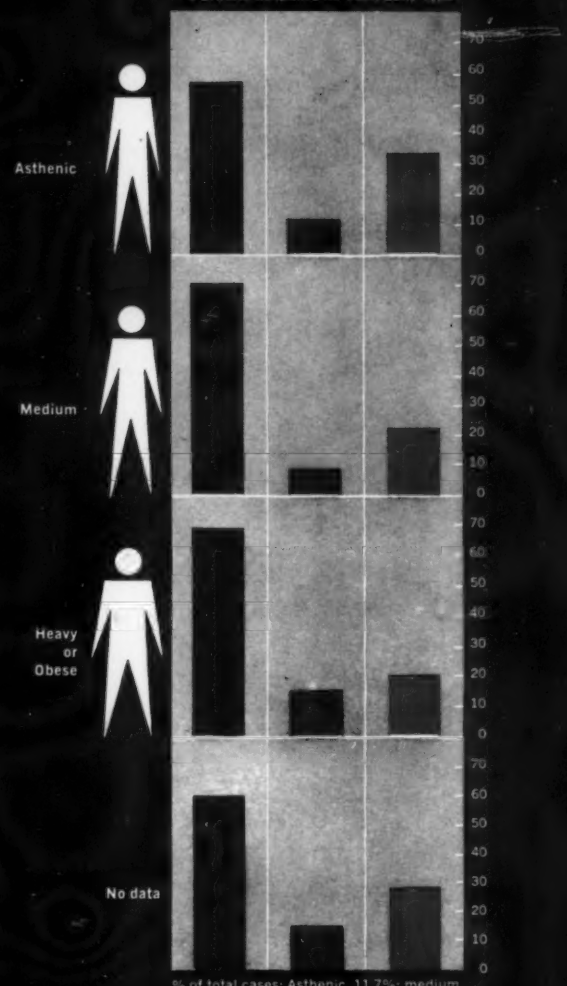
Throughout this report, the character of a patient's diabetes control prior to and after institution of Orinase therapy is classified as "excellent," "good," "fair," "poor," or "failure," according to the assessment of laboratory and clinical findings.

Table II. Correlation of Orinase Response with Age at Time of Onset of Diabetes



% of total cases: >40, 83.7%; 20-39.9, 12.2%; <20, 3.0%; no data, 1.1%

Table III. Distribution of Types of Body Build and Their Correlation with Orinase Response



% of total cases: Asthenic, 11.7%; medium, 45.0%; heavy or obese, 30.3%; no data, 13.0%

Excellent-good

Fair

Combined failures*

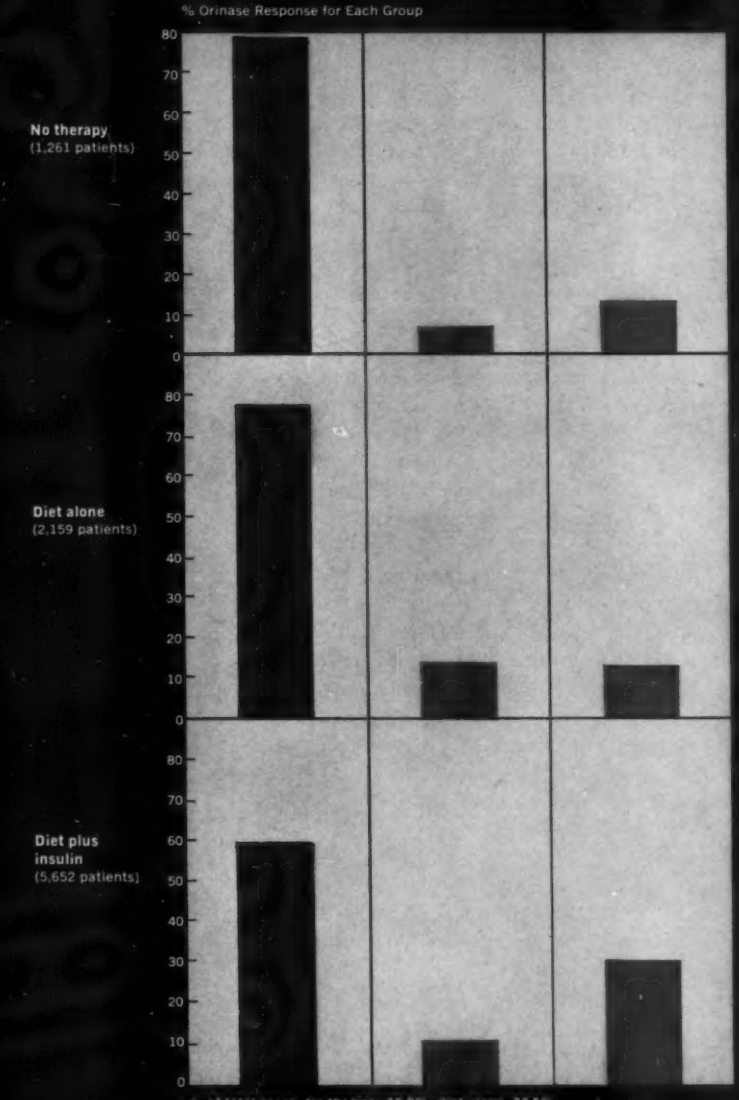
Unreported

*Note: Combined failures include those patients who showed no initial response to a therapeutic trial of Orinase (primary failure) and those who after a period exceeding 1 month of satisfactory or fair control subsequently lost responsiveness to oral therapy (secondary failure). Of the total of 468 instances of secondary failure (5.1%) in the entire series of patients under study, only 222 cases of idiopathic secondary failure (2.4%) occurred. The other 246 could be readily attributed to gross dietary negligence, intercurrent infection (pneumonia, acute pyelonephritis, rectal abscess, etc.) or a severe emotional upset (death of a spouse, etc.).

How does previous management correlate with the subsequent response to Orinase?

Patients who had previously been on no routine of treatment at all responded just about the same to Orinase as those who had been maintained on diet alone. The insulin-treated group produced a lesser incidence of highly satisfactory control, as would be expected with patients exhibiting a more severe form of diabetes. Further analysis of the diet-treated and the insulin-treated groups follows.

Table IV. Correlation of Prior Therapeutic Status with Orinase Response



% of total cases: No therapy, 13.8%; diet alone, 23.5%; diet plus insulin, 61.7%; unreported, 1%.

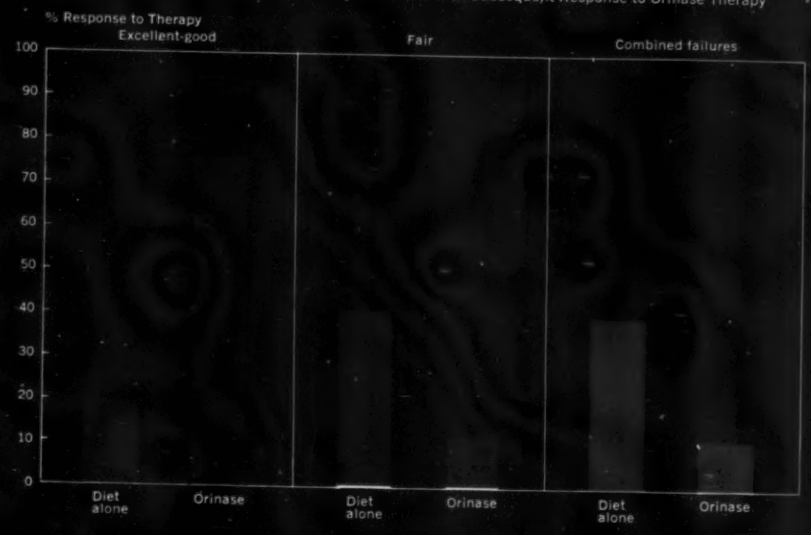
What results can be anticipated when diet-treated diabetics are converted to Orinase?

It is evident that better control of diabetes can be achieved with Orinase than by diet alone.

What results can be anticipated when insulin-treated patients are converted to Orinase?

Of 5,233 patients previously treated with insulin, a good to excellent response had been secured with injection therapy in 52.8% (2,819 patients). When these 2,819 patients were placed on Orinase, 73% (2,071 patients) still had a good to excellent response on the oral drug. Of even greater significance is the fact that almost half (49%) of the patients with no more than a fair response to insulin, and as many as 29% of those with a poor response to insulin, experienced an obvious upgrading in quality of blood sugar control to good or excellent status when switched to Orinase.

Table V. Correlation of Quality of Control by Diet Alone with Subsequent Response to Orinase Therapy

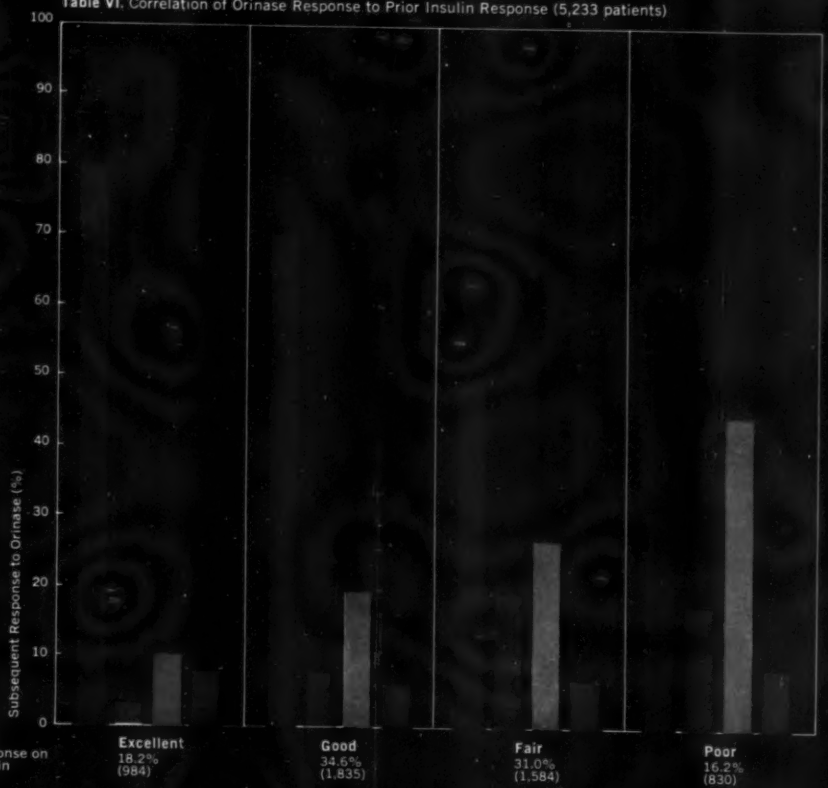


Excellent-good

Fair

Combined failures: See Note, **Table III.**

Table VI. Correlation of Orinase Response to Prior Insulin Response (5,233 patients)



Excellent-good

Fair

Primary failure

Secondary failure: See Note, **Table III.**

Prior Response on Insulin	Excellent	Good	Fair	Poor
	18.2% (984)	34.6% (1,835)	31.0% (1,584)	16.2% (830)

How does previous insulin dosage affect the response to Orinase?

As the insulin requirement of a diabetic patient often serves as a rough index of the severity of his disease, it is not surprising to find that the frequency of successful response to Orinase therapy is significantly higher with lesser insulin requirements. Nonetheless, almost half of the patients requiring 31-40 units of insulin daily secured a good to excellent response when switched to Orinase.

How does the duration of prior insulin therapy affect Orinase response?

The duration of previous therapy on insulin does not seriously limit the successful use of Orinase.

Table VII. Correlation of Prior Insulin Dose with Orinase Response

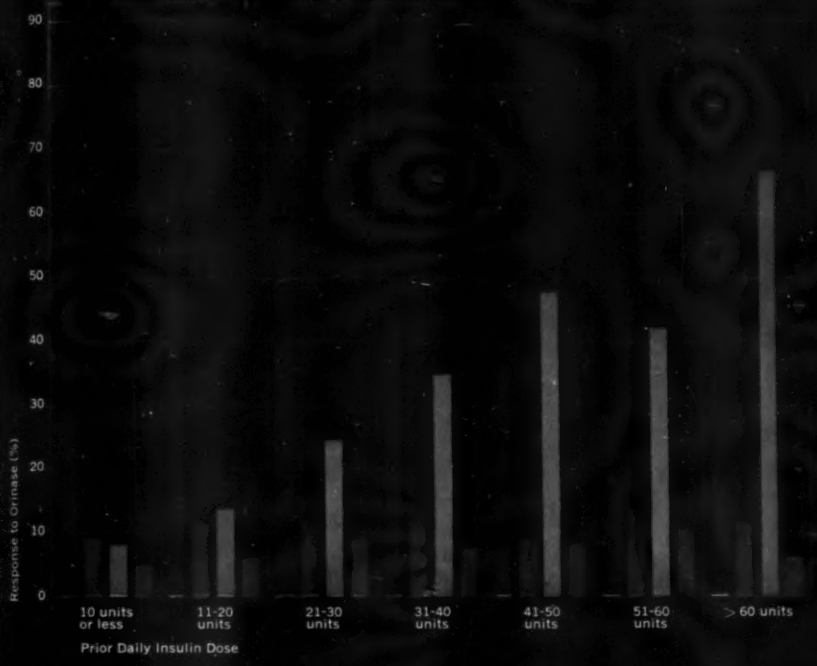
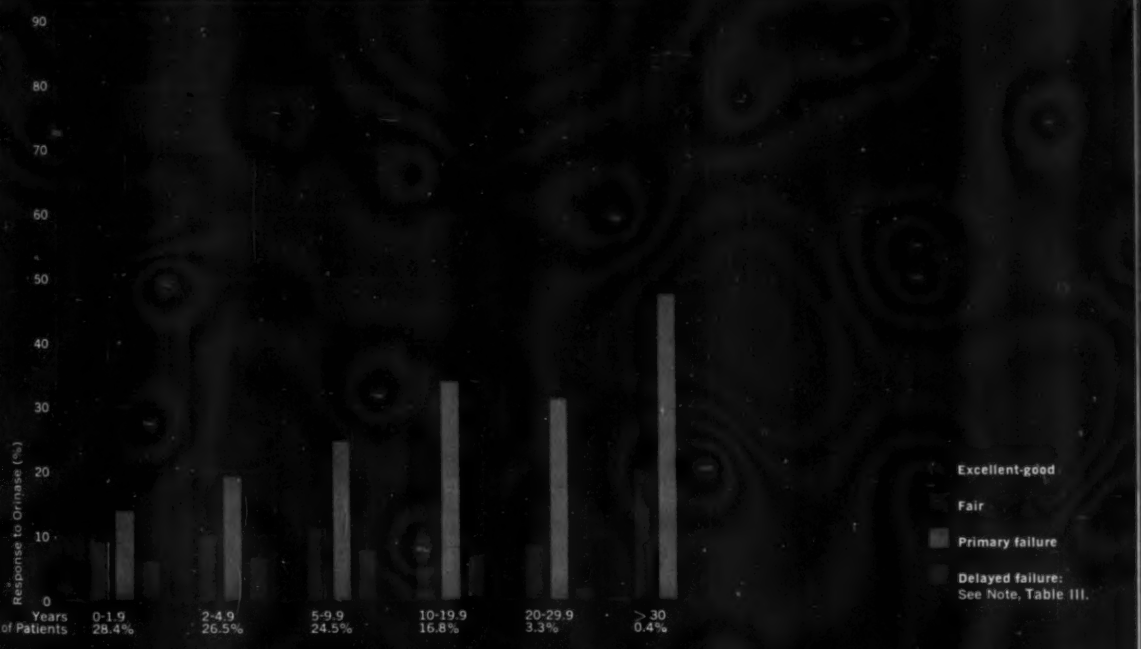


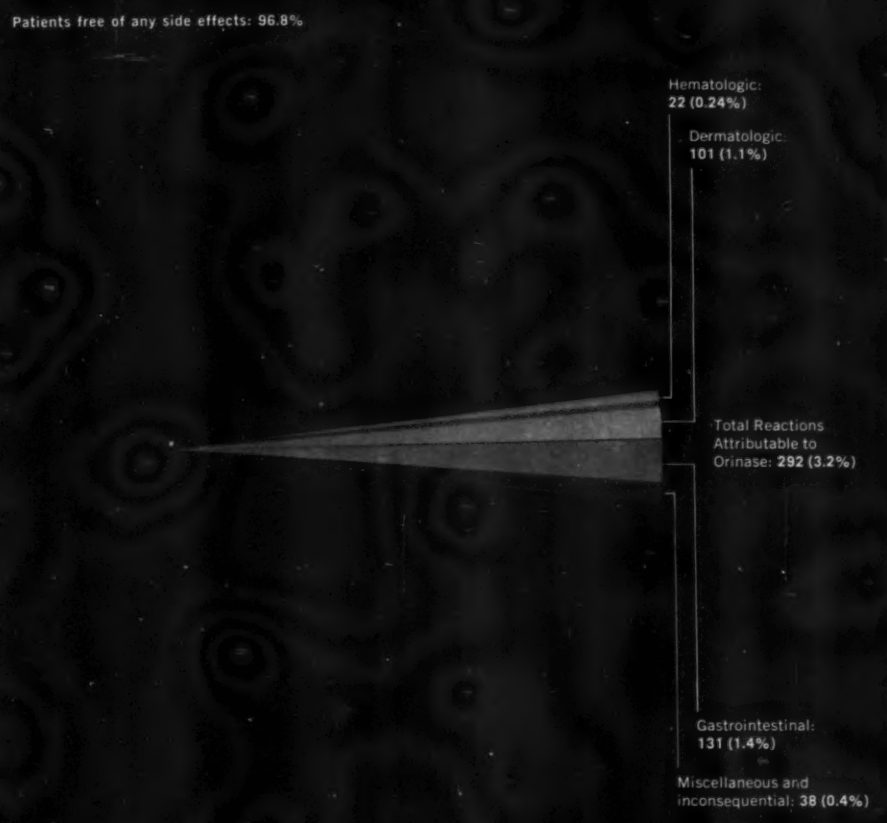
Table VIII. Correlation of Duration of Insulin Therapy with Orinase Response



What is the incidence of side effects associated with Orinase?

A total of 292 reactions was reported to have occurred in the course of Orinase administration, representing a gross reaction incidence of 3.2%. Withdrawal of Orinase was considered necessary in only 140 instances, or 1.53% of the total series. The significance of this low incidence is heightened by the fact that 57% of the 9,168 patients in this analysis were maintained on Orinase therapy for a minimum of 6 months to more than 28 months.

IX. Summary of Side Effects Reported as Occurring
sociation with the Use of Orinase


Patients free of any side effects: 96.8%
Hematologic: 22 (0.24%)
Dermatologic: 101 (1.1%)
Total Reactions Attributable to Orinase: 292 (3.2%)
Gastrointestinal: 131 (1.4%)
Miscellaneous and inconsequential: 38 (0.4%)

Type of Reaction	Total Cases	Orinase Therapy: Continued	Orinase Therapy: Interrupted	Orinase Therapy: Discontinued	Disposition Unreported
Hematologic	22 (0.24%)	9	2	11 (0.12%)	0
Dermatologic	101 (1.1%)	36	14	48 (0.52%)	3
Gastrointestinal	131 (1.4%)	53	14	63 (0.7%)	1
Hepatic	0	–	–	–	–
Renal	0	–	–	–	–
Thyroid	0	–	–	–	–
Miscellaneous and inconsequential	38 (0.4%)	16	3	18 (0.2%)	1
Total Reactions Attributable to Orinase	292 (3.2%)				
Total Reactions for which Orinase Discontinued				140 (1.53%)	

Better control of diabetes

Orinase-responsive patients show more stable blood sugar levels and less glycosuria on Orinase than on insulin. Because Orinase acts via *endogenous* insulin, daily control of diabetes is smoother; "peaks and valleys" typical of exogenous insulin are leveled out.

Objective advantages

Greater freedom from hypoglycemia

Orinase is a true *eu*glycemic agent, once maintenance dosage has been established, it lowers blood sugar to normal levels, but almost never below normal. And because Orinase is rapidly inactivated in the body, drug levels never cumulate.

Better blood sugar control

Many patients who respond poorly to insulin experience marked improvement of blood sugar control when they are transferred to Orinase. Even in certain labile diabetics, who cannot be controlled on Orinase alone, the use of Orinase as a supplement to insulin therapy may effect stabilization of the diabetic condition and permit a reduction in insulin dosage.

Side effects— few and minor

Side effects attributable to Orinase occur in about 3% of cases, and only half of these necessitate withdrawal of Orinase. Most common are mild gastrointestinal upsets or transient skin rash.

No known toxicity

Careful observations of large series of patients maintained on Orinase for more than two years revealed no damage to the liver, blood, kidneys, or pancreas. Orinase is not goitrogenic.

Painless management of diabetes

Simple, easy, oral administration eliminates subcutaneous fat atrophy and frequent allergic reactions to insulin.

No increase in insulin requirements

Even after prolonged Orinase therapy, patients scarcely ever show any increase in insulin requirements. In fact, such increase on Orinase is *less common than on insulin.*

No impairment of diabetic status

Orinase therapy does not aggravate the underlying diabetic pathology. No evidence of aggravation of retinopathy, nephropathy, or neuropathy has been found.

Orinase tends to restore emotional balance

Diagnosis of diabetes, usually coming late in life and carrying with it a long sentence of daily fear and anxiety, profoundly upsets the emotional balance of the average patient. Adjustment to radical changes in daily living is difficult. Daily injections, special meal schedules, and new limitations on activities make the patient feel "set apart." Oral therapy simplifies life, brings it closer to normal, helps restore a cheerful, hopeful outlook.

Subjective advantages

Sense of personal freedom regained on Orinase

No longer tied to sterilizing apparatus, nearest restaurant, and rigid schedules, a diabetic on Orinase can enjoy travel and a variety of personal activities, free from the tyranny of the clock and the threat of hypoglycemia.

Urticaria?

Dimetane works to relieve the symptoms in urticarial reactions, as it does in allergic rhinitis, atopic and contact dermatitis. The summary conclusion of extensive clinical studies to date: Dimetane provides unexcelled antihistaminic potency with minimal side effects—in the whole gamut of allergic disorders. For your patient with allergic symptoms prescribe Dimetane, available in the following forms: ORAL: Extentabs® (12 mg.), Tablets (4 mg.), Elixir (2 mg./5 cc.). PARENTERAL: Dimetane-Ten Injectable (10 mg./cc.) or Dimetane-100 Injectable (100 mg./cc.). A. H. Robins Co., Inc., Richmond 20, Virginia. Ethical Pharmaceuticals of Merit Since 1878.

Robins

Dimetane!

(PARABROMDYLAMINE MALEATE)®

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.

• HOYER KARTOP LIFT

DESCRIPTION: Patients in wheel chairs can be helped in and out of automobiles with this lift, which can be quickly mounted on top of the car and left in place permanently if desired. To use, a sling is slipped under the patient and attached to the lifting arm. The patient is then raised from the chair by pumping a handle. A roller on the lifting arm facilitates his entrance into the car, and a release valve controls his descent onto the seat. The procedure is reversed when he leaves car. Heavy-duty suction cups and adjustment clamps hold the lift securely in place and eliminate the need for mounting holes or special attachments. Extra supports are available for patients whose disabilities require them.
PRODUCER: Everest & Jennings, Inc., Los Angeles.

• VIGRAN® CHEWABLES

PURPOSE: Nutritional supplement.
COMPOSITION: Each fruit punch-flavored soft tablet contains 125 per cent of the minimal daily requirements of vitamins A, D, B_1 and B_2, plus other essential vitamins.
HOW SUPPLIED: Bottles of 30 and 90.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• STREPTOMYCIN SULFATE SOLUTION

PURPOSE: Antibiotic.
DOSAGE AND ADMINISTRATION: Intramuscularly.
HOW SUPPLIED: 5 gm. in 10 cc. multiple-dose vials.
PRODUCER: Philadelphia Ampoule Laboratories, Philadelphia.

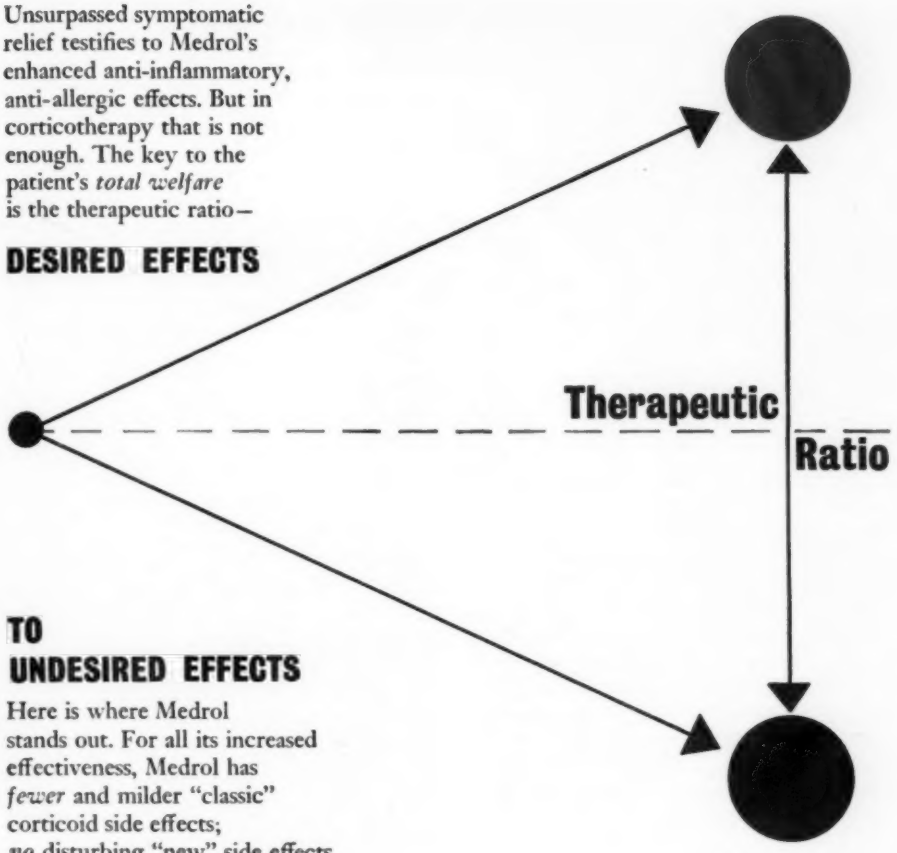
• PROZINE®

PURPOSE: To relieve the symptoms of emotional disturbance.
COMPOSITION: Each capsule contains 200 mg. of meprobamate and 25 mg. of promazine hydrochloride.
DOSAGE AND ADMINISTRATION: 1 or 2 capsules, three or four times daily.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Wyeth Laboratories, Philadelphia 1.

(Continued on page A-154)

Unsurpassed symptomatic relief testifies to Medrol's enhanced anti-inflammatory, anti-allergic effects. But in corticotherapy that is not enough. The key to the patient's *total welfare* is the therapeutic ratio—

DESIRED EFFECTS



TO UNDESIRED EFFECTS

Here is where Medrol stands out. For all its increased effectiveness, Medrol has *fewer* and milder "classic" corticoid side effects; *no* disturbing "new" side effects such as muscle weakness. Whenever corticotherapy is indicated, remember that Medrol has the *best therapeutic ratio in the steroid field.*

Medrol hits the disease, but spares the patient

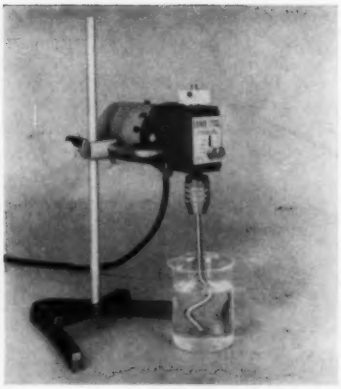
The best therapeutic **ratio in the steroid field makes**

Medrol*

the choice of physicians who consider the total welfare of their patients

*Trademark, Reg. U. S. Pat. Off.—methylprednisolone, Upjohn

Upjohn The Upjohn Company, Kalamazoo, Michigan



• MOTOR STIRRER

DESCRIPTION: Consistent stirring action at selectively controlled speeds enables this laboratory unit to stir highly viscous liquids at rates ranging from 100 to 1500 rpm. A three jaw Jacobs-type chuck facilitates quick changes of metal or glass stirring rods which measure ¼ to ⅜ in. in diameter. The rod is mounted in a hollow shaft which is easily adjusted to any desired height. A special rod for mounting in a right-angle clamp permits pivoting of the unit for stirring at various angles. The 1/50 h.p. motor operates on 115 V, AC, 50 to 60 cycles.
PRODUCER: Central Scientific Company, Chicago.

• ELASTIKON® ADHESIVE TAPE

DESCRIPTION: This porous elastic adhesive tape allows perspiration to escape from the skin through holes in the adhesive mass. Supplied in flesh tone, the tape comes in rack rolls in 1, 2, 3 and 4 in. widths.
PRODUCER: Johnson & Johnson, New Brunswick, N. J.

• RUBRAMIN® PC

PURPOSE: Vitamin B_{12} therapy.
COMPOSITION: Cyanocobalamin.
DOSAGE AND ADMINISTRATION: Intramuscularly, subcutaneously or intravenously.
HOW SUPPLIED: 30, 50 or 100 μg. per cubic centimeter in 10 cc. vials; 1000 μg. per cubic centimeter in 1 cc. and 10 cc. vials.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• ISOPRO AND ISOPRO H.P.

PURPOSE: Oral bronchodilator.
COMPOSITION: Isopro: 0.5 per cent isopropylarterenol. Isopro H.P.: 0.4 per cent isopropylarterenol, 2 per cent phenylephrine hydrochloride and 10 per cent propylene glycol.
INDICATIONS FOR USE: Isopro: symptomatic treatment of bronchial spasms. Isopro H.P.: bronchial asthma and emphysema.
DOSAGE AND ADMINISTRATION: To be inhaled.
HOW SUPPLIED: Isopro: 10 cc. and 50 cc. dropper bottles. Isopro H.P.: 10 cc. dropper bottles.
PRODUCER: Philadelphia Ampoule Laboratories, Philadelphia.

• US-1 UNIVERSAL SHIELD

DESCRIPTION: Designed to handle a wide variety of radiation counting work, this unit accepts any basic nuclear detector for gamma scintillation, GM, and proportional counting. A clock-stop mechanism and scale indicate each centimeter of vertical movement, slides are spaced 1 cm. on center, and 2 in. of lead surrounds the detector on all sides. The unit is 12 in. high and 11 in. in diameter at the base. Standard equipment includes three sample and three absorber slides, which accommodate either samples or absorbers 1 or 2 in. in diameter. Optional slides, which permit manual and semiautomatic operation and chromatogram strip counting, and detectors with adapters for interchangeable use without adjustment to the basic shield are also available.
PRODUCER: Nuclear Measurements Corporation, Indianapolis.

(Continued on page A-156)

for your ambulant asthmatic . . . "Air in a hurry!"

Nephenalin®, the square purple tablet that relieves asthma with nebulizer speed for 4 full hours, offers convenience and reassurance to your ambulant asthmatic patient. Placed under the tongue, the NEPHENALIN tablet quickly releases 10 mg. of Isoproterenol HCl, the potent homologue of epinephrine, for immediate opening of the airway. Swallowed, the NEPHENALIN tablet provides theophylline (2 gr.), ephedrine (3/8 gr.) and phenobarbital (1/8 gr.), for sustained protection from asthmatic seizure. NEPHENALIN is available for your prescription in bottles of 20 and 100 tablets. Also available: NEPHENALIN PEDIATRIC. *Thos. Leeming & Co. Inc.* NEW YORK 17, N.Y.

• LD-25 CONTAINER

DESCRIPTION: This 25 liter cryogenic container for the transport and storage of liquid nitrogen is constructed of welded aluminum. Insulation cuts nitrogen evaporation to a 5 per cent maximum, and, because of its 1½ in. necktube diameter, the container is usable as a freezing and preserving refrigerator for small biologic specimens. Accessories include a dipper for removing small quantities, a pressure withdrawal tube, and a shock-absorbing roller base. The container is 22¾ in. high and 15¼ in. in diameter, and weighs 19 lb. when empty.
PRODUCER: Linde Company, Division of Union Carbide Corporation, New York.

• TRACHEOTOMY TUBE SET

DESCRIPTION: Made of inert plastic, the tube is available in sizes 3 through 7, each in long, medium, short and extra-short lengths. The complete set includes one outer tracheotomy tube, two inner cannulae which snap into place in the outer tube, and an obturator and a plug for use when the patient is being prepared for decannulization or when the tube is required for suction but not for ventilation.
PRODUCER: R. A. Hawks Division, Sierra Engineering Company, Sierra Madre, Calif.

• KENALOG®-S LOTION

PURPOSE: Topical corticosteroid-antibiotic.
COMPOSITION: Kenalog (triamcinolone acetonide) and SPECTROCIN® (neomycin and gramicidin) in lotion form.
INDICATIONS FOR USE: Atopic, seborrheic or contact dermatitis, neurodermatitis and other eczematous dermatoses.
HOW SUPPLIED: 7.5 cc. plastic squeeze bottles.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• DERMPAK THERAPEUTIC GLOVES

DESCRIPTION: Used for applying wet packs in dermatoses of the hand, these gloves are made of 12-ply preshrunk, sterilized, quilted gauze, and may be washed and re-used. They are available in small, medium and large sizes.
PRODUCER: Dermpak Corporation, St. Paul.

• CORTISPORIN® LOTION

PURPOSE: Broad-spectrum antibiotic action in skin conditions.
COMPOSITION: Each cubic centimeter contains:

AEROSPORIN® (Polymyxin B sulfate)	10,000 units
Neomycin sulfate	5 mg.
Hydrocortisone (1%)	10 mg.

in a water-miscible lotion base.
INDICATIONS FOR USE: Pustular acne, dermatitis, eczema, intertrigo and anogenital pruritus.
DOSAGE AND ADMINISTRATION: As needed.
HOW SUPPLIED: 10 cc. bottles.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y.

(Continued on page A-158)

Convenient information for physicians starting diabetic patients on

DIABINESE

simple once-a-day dosage in practice

During the initial control period, the patient should check his urine at frequent intervals, and report at least once weekly for review of symptoms, physical examination, urine and/or blood examination for glucose.

The New Patient *(no previous antidiabetic therapy)*

1. Initial daily dose 500 mg. (2 tablets of 250 mg. each) with breakfast.

2. In elderly patients, initial dose 250 mg. (1 tablet) daily.

3. CONTROL PERIOD

(a) If blood sugar reaches normal levels after three to seven days, or if glycosuria disappears, lower daily dose of 500 mg. to a level between 250 mg. (1 tablet) and 375 mg. (1½ tablets of 250 mg.) with breakfast daily. In elderly patients, dosage may be reduced to as low as 100 mg.

(b) If hyperglycemia or glycosuria persists or develops, increase the daily dose from 500 mg. to 625 mg. (2½ tablets of 250 mg.) with breakfast daily. In elderly patients, dosage should be increased from 250 mg. according to patient response.

(c) Continue weekly adjustments during first month of therapy until maintenance dose has been established. Adjustments below 250 mg. daily are best made in steps of 100 mg. (one 100 mg. tablet). The maintenance dose may occasionally be as low as 100 mg. (one 100 mg. tablet daily) or, rarely, as high as 1.0 Gm. (four 250 mg. tablets) daily. Do not exceed daily dose of 1.0 Gm.

Transfer of Patient from Insulin

1. If patient is taking 40 or less units of insulin daily and gives no history of severe or "brittle" diabetic response, discontinue insulin and replace with DIABINESE as in The New Patient.

2. Complete control period as for The New Patient. Priming ("loading") doses should not be used.

3. If patient is taking more than 40 units of insulin daily, or shows evidence of severe or brittle diabetes, reduce insulin dose by 50 per cent and initiate DIABINESE therapy as for The New Patient. Further reduction of insulin dosage depends on patient response.

Transfer of Patient from Other Oral Medication

Where less than satisfactory control has been achieved with other oral medication, or where a change to once-a-day dosage is desired, DIABINESE may be successfully substituted. Such a transfer may be made by discontinuing previous oral medication, substituting DIABINESE, and continuing control period as for The New Patient. Avoid priming doses.

The clinical safety of DIABINESE has been established by more than two years' trial. By adherence to the above dosage schedule, side effects of DIABINESE will generally be infrequent, mild, and transient.

Pfizer

DIABINESE®

brand of chlorpropamide

once-a-day dosage

THE MOST EFFECTIVE ORAL ANTIDIABETIC AVAILABLE

SUPPLIED: *Tablets*, 250 mg., bottles of 60 and 250, white, scored. 100 mg., bottles of 100, white, scored.

Science for the world's well-being Pfizer PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N. Y.

• STERAZOLIDIN®

PURPOSE: Low-dosage steroid therapy.
COMPOSITION: Each capsule contains:

Prednisone	1.25 mg.
BUTAZOLIDIN®	50 mg.
Dried aluminum hydroxide gel	100 mg.
Magnesium trisilicate	150 mg.
Homatropine methylbromide	1.25 mg.

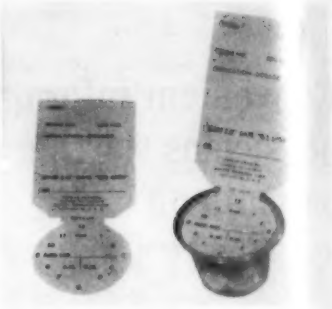
INDICATIONS FOR USE: Chronic rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and acute rheumatoid conditions.
DOSAGE AND ADMINISTRATION: As needed.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Geigy Pharmaceuticals, Ardsley, N.Y.

• ACE® MEDICAL GLOVE

DESCRIPTION: This two finger, single-use interchangeable glove is made of thin, tough, form-fitting polyethylene. It was formerly known as the Scott disposable glove. The gloves are available in boxes of 1 gross.
PRODUCER: Becton, Dickinson and Company, Rutherford, N. J.

• DELUTEVAL

PURPOSE: Hormonal therapy.
COMPOSITION: Each ampule contains hydroxyprogesterone caproate (DELALUTIN®) and estradiol valerate (DELESTROGEN®).
INDICATIONS FOR USE: Dysfunctional uterine bleeding, amenorrhea and other disturbances of the menstrual cycle, and in habitual or threatened abortion.
DOSAGE AND ADMINISTRATION: Intramuscularly.
HOW SUPPLIED: 2 cc. ampules.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.



• PILL-PACK MEDICATION DISPENSER

DESCRIPTION: This disposable plastic Pill-Pack, featuring a Safety-Seal lid with detachable medicine card, holds up to 12 pills or ½ fl. oz. The medicine card has spaces for patient's name, room and bed number; medication and directions for administration, and the doctor's name. The Safety-Seal lid also has space for patient's name and directions for administration. A lightweight, plastic carrying tray for up to 25 containers is available.
PRODUCER: Caddie Creations, Chicago.

• AUTOMATIC BLOOD PRESSURE RECORDER (Modification of Model 110)

PURPOSE: To measure rapid changes in blood pressure without arterial puncture.
DESCRIPTION: An auxiliary plug-in control circuit converts this instrument into a dynamic blood pressure recorder which can measure systolic or diastolic pressures at intervals of three to four seconds. Features incorporated in the unit include noise discrimination, safety devices, method of registration, and an alarm system to warn of a critical drop in systolic pressure.
PRODUCER: Gilford Instrument Laboratories, Inc., Elyria, Ohio.

SATURDAY

1959 FEBRUARY 1959						
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► PICTORIAL HANDBOOK OF FRACTURE TREATMENT

By Edward L. Compere, M.D., Professor and Chairman, Sam W. Banks, M.D., Associate Professor, and Clinton L. Compere, M.D., Associate Professor, Department of Orthopaedic Surgery, Northwestern University Medical School, Chicago. Ed. 4. 448 pages with 268 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $7.50.

The medical profession's overwhelming acceptance of this handbook created the need for a new, up-to-date edition. While most orthopedic principles have remained basically unchanged, newer operative and conservative technics have been successfully introduced since the last edition was published.

This text is directed primarily to the medical student, orthopedic resident and general practitioner. Although it is not sufficiently comprehensive for the student, it will direct his concept of orthopedics toward basic principles and general conservative treatment. It is well written, easily read and has excellent radiographic reproductions and descriptive drawings.

Sequelae of orthopedic injury or disease often have far-reaching medicolegal aspects. This source book will assist the physician in determining what long-range treatment to employ and whether or not satisfactory results may be expected. The text also emphasizes the need in certain instances for orthopedic consultation and presents a comparative basis for the necessity of seeking additional opinion in cases of injury.

E. H. O'P.

► DIAGNOSTIC BACTERIOLOGY

By Isabelle G. Schaub, A.B., Assistant Professor of Microbiology, The Johns Hopkins University School of Medicine, M. Kathleen Foley, M.A., Assistant Professor of Biological Sciences, College of Notre Dame of Maryland, Baltimore, Elvyn G. Scott, M.T., Bacteriologist-in-Charge, Department of Bacteriology, The Delaware Hospital, Wilmington, and W. Robert Bailey, Ph.D., Associate Professor of Biological Sciences, University of Delaware, Newark. Ed. 5. 338 pages, illustrated. 1958, The C. V. Mosby Company, St. Louis. $4.75.

Four editions of this manual for use in clinical bacteriology laboratories were prepared by Schaub and Foley; this fifth edition has been prepared by Scott and Bailey. The original material and format have been retained, with revisions to bring the book up to date. Four new chapters have been included describing the plate dilution method for determining antibiotic susceptibility, the determination of the antibacterial level of serum during antibiotic therapy, new serologic tests (antistreptococcin O and C-reactive protein), and the handling of specimens for the laboratory diagnosis of virus diseases. There is also a new section on the identification of fungi which cause systemic infections.

The absence of illustrative material is quite noticeable; there are only 14 line drawings, illustrating mycotic infections. However, the technics are clearly described, and the manual will prove useful to laboratory technicians.

A. H. S.

(Continued on page A-188)

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► RADIOACTIVE ISOTOPES IN CLINICAL PRACTICE

By Edith H. Quimby, Sc.D., Professor of Radiology, Columbia University College of Physicians and Surgeons, Sergei Feitelberg, M.D., Director, Physics Department, and Solomon Silver, M.D., Chief, Thyroid Clinic, Mount Sinai Hospital, New York. 451 pages with 97 illustrations. 1958, Lea & Febiger, Philadelphia. $10.00.

The authors of this volume, all specialists in their particular fields, have been conducting comprehensive courses in the clinical uses of radioisotopes for the past four years.

As might be expected, the main emphasis is on the fundamentals of nuclear physics and instrumentation. Dr. Quimby presents the first section, which is on basic physics; Dr. Feitelberg reviews instrumentation and laboratory methods, and Dr. Silver discusses clinical applications. The result is a thorough analysis of radioactivity, directed toward the physician actively engaged in the medical uses of radioisotopes, particularly the therapeutic applications.

Although the book is probably not appropriate for the physician only casually interested in medical radioisotopes, it is so clearly and sensibly written that the reader need have no fear if he has forgotten his college physics and mathematics. Dr. Quimby carefully leads him through the arithmetic of the radiation effect of various radioisotopes and then documents the equations with specific examples, such as P^{32}, I^{131} and Na^{24}. Since the amount of a radioactive substance to be given a patient depends not only on the biologic goal but also on the deleterious effect of the radiation, a thorough review of the biologic effects of ionizing radiation is presented. This is followed by a chapter on how to minimize radiation hazards to personnel administering radioactive materials and caring for patients. From the anatomy of the atom to the disposal of radioactive wastes, Dr. Quimby holds the interest of the reader with her clear and relaxed style.

In common with his coauthors, Dr. Feitelberg is more interested in the principles guiding the correct use of radioisotopic equipment than in the specific details of their everyday management. The result is a comprehensive discussion of statistical errors, advantages and shortcomings of decade and binary scalers, principles of collimation, and applications of the inverse-square law. The advantages of the binary system over the usual decimal system of numbers, forced on us in this age of electronic computers, are convincingly described. The particularly detailed discussion of measurement of beta rays is perhaps a forward look to the day when isotopes emitting only such rays become more useful medically.

Dr. Silver skillfully describes the actual medical uses of various radioactive substances. The emphasis is on radioiodine and the thyroid gland, for investigation of the thyroid is quantitatively the main function of the radioisotopic laboratory today. Other commonly performed isotopic tests, such as those utilizing erythrocytes labeled with $chromium^{51}$ or vitamin B_{12} labeled with $cobalt^{60}$, are briefly reviewed.

C. A. O.

► SURGERY OF THE HEAD AND NECK

By Robert A. Wise, M.D., Associate Clinical Professor of Surgery, and Harvey W. Baker, M.D., Clinical Instructor of Surgery, University of Oregon Medical School, Portland. 319 pages with 82 plates. 1958, The Year Book Publishers, Inc., Chicago. $9.75.

A wide variety of surgical procedures used in managing lesions about the head and the neck, including those of plastic surgery, are diagrammatically illustrated. Anatomic detail is not included, but any surgeon who contemplates operating in this region should be acquainted with the normal anatomic relationships well in advance of considering the operation to be used.

The text includes notes on diagnosis, biopsy procedures, preoperative and postoperative care and many points of practical importance in dealing with this problem. Discussions cover infections, congenital lesions, benign and neoplastic tumors and lesions of the intra-oral cavity, sinuses, pharynx, larynx, mandible, thyroid and parotid glands and the lateral part of the neck. The authors recommend, for the most part, their own surgical approaches; however, they consider fairly the other methods.

The handbook is a surgical treatise and does not include historical or statistical data or information regarding prognosis. There is no bibliography. The book can be highly recommended to the student for his study and to the surgeon as a reference.

O. H. B.

(Continued on page A-190)

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► ANATOMY FOR SURGEONS
The Back and Limbs

By W. Henry Hollinshead, Ph.D., Professor of Anatomy, Mayo Foundation, and Head, Section of Anatomy, Mayo Clinic, Rochester, Minnesota. Vol. 3. 901 pages with 785 illustrations. 1958, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $23.50.

This is the final volume of an outstanding surgical-anatomic presentation. It is developed around specific chapters, in which the author presents information from surgeons who have specialized in treating one particular portion of the body. The book is an excellent reference for basic anatomic knowledge, encompassing vast amounts of relative information, and including an extensive bibliography. It is intended to serve as a guidance text and, as such, contains many illustrations and diagrams that are readily understood, have simple features, and function as effective communication.

Some readers may prefer the brevity and more delicate illustrations that have been presented in other textbooks of anatomy, but most will find little to criticize in this distinguished book.

E. H. O'P.

► SOCIAL PSYCHIATRY IN ACTION
A Therapeutic Community

By Harry A. Wilmer, M.D., Naval Medical Research Institute, Bethesda. 373 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $8.75.

The effort of psychiatrists to benefit the mentally ill has continuously produced new concepts to be tried and evaluated.

Dr. Wilmer made excellent use of his tour of duty in the United States Navy to institute his firm beliefs that mental hospitals can be managed in a far less rigid manner and that a more natural setting can be provided in order to decrease the feeling of isolation and enhance the self-respect of the patient as a human being. This was accomplished at the Oakland Naval Hospital, and was certainly largely due to Dr. Wilmer's contagious enthusiasm, basic warmth, and the obvious respect he felt for his patients. Restraints and sedatives were discarded, and emphasis was placed on self-expression within a group setting, with the interplay of the group's emotions showing the way back to successful adjustment outside the hospital.

The author's refreshing style makes this book read like an interesting adventure. At the same time, it is packed with fascinating dynamics and offers a frank discussion of the staff and its role in relationship to the patient.

This book will give added impetus to the movement toward establishing therapeutic communities in many places throughout the country. The United States Navy's high regard and enthusiasm for Dr. Wilmer's work are reflected in the preface by Rear Admiral Hogan, Surgeon General, United States Navy.

E. M. L.

► SYSTEMIC OPHTHALMOLOGY

Edited by Arnold Sorsby, Research Professor in Ophthalmology, Royal College of Surgeons and Royal Eye Hospital, London, England, with 34 contributors. Ed. 2. 682 pages with 277 illustrations and 24 color plates. 1958, The C. V. Mosby Company, St. Louis. $25.00.

The first edition of this book was designed to cover more than just the medical aspects of eye disease, "for the general aspects of eye disease carry surgical, obstetric, metabolic, dermatologic and other implications no less than those of a purely medical character." The publication of this new edition has made it possible to bring the text up to date.

Unlike the usual textbook, this volume contains papers on selected subjects by collaborators chosen for their special interest in and knowledge of systemic diseases by category. Where the distinction of disease by diagnosis allows application of general terms, important material has been included with minimal overlapping.

The book is divided into six parts: prenatal pathogenic influences; inflammation, allergic reactions and infections; nutritional, metabolic and endocrine disturbances; central nervous system; cardiovascular systems; and other general disturbances. As the title implies, refraction, surgical technics, anatomy and physiology are not considered. The text includes a wealth of material that also is available in journals of ophthalmology published during the past 10 years; as arranged for this volume it is complete, orderly and authoritative.

W. L. B.

(Continued on page A-192)

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► THE ACUTE ABDOMEN

By William Requarth, M.D., Clinical Assistant Professor of Surgery, University of Illinois College of Medicine, Chicago. Ed. 2. 313 pages with 87 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $6.50.

Few changes have been made in this book since the first edition, "The Diagnosis of Acute Abdominal Pain," was published in 1953. The primary difference is that it now contains more information concerning the principles of surgical treatment.

Excellent discussions of the examination of the abdomen and the differential diagnosis of the various acute conditions are presented. Although intended primarily for surgeons, this well-written text will be of interest and benefit to all who practice medicine.

R. V. R.

► THE MANAGEMENT OF EMERGENCIES IN THORACIC SURGERY

By John Borrie, F.R.A.C.S., Thoracic Surgeon, Dunedin Hospital, Dunedin, New Zealand. 340 pages, illustrated. 1958, Appleton-Century-Crofts, Inc., New York. $10.00.

There has long been a need for a short, concise discussion of the problem of thoracic surgical emergencies. This volume goes a long way toward filling this need. In fact, it goes further than its title suggests. Fundamentals which are essential to the management of any thoracic surgical problem are included. Likewise, the subsequent management of conditions which first present themselves as acute emergencies is discussed.

The subject matter is presented in a simple, straightforward fashion, with the outline form used in many instances. A large number of clear illustrations are included to supplement the text. Particularly helpful to the intern, resident or general physician are some of the early chapters which discuss in detail the technic of thoracentesis, institution of intercostal drainage, bronchoscopy and tracheotomy.

The bulk of the text deals with common emergencies which may involve the lung, esophagus, diaphragm, mediastinum and heart. The chapter on preoperative and postoperative care of the thoracic surgical patient is particularly helpful, although one might question the necessity or advisability of frequent aspiration of the postpneumonectomy space. Another point of discussion might be the author's management of spontaneous pneumothorax. This reviewer has successfully used a malleable intercostal needle for purposes of aspiration and would not favor such free use of thoracoscopy and pleural poudrage as is advocated in the text. Perhaps the author is unnecessarily pessimistic regarding the efficacy of fibrinolytic agents in the treatment of hemothorax.

Differences of opinion are bound to exist within the scope of a book such as this. Nevertheless, this work is a fine addition to the growing list of texts concerned with thoracic surgical problems. Because the practical side of thoracic surgical management is so nicely summarized, the book will be of particular help to those in training and to those who are only occasionally confronted with a thoracic surgical problem.

F. H. E.

► LESIONS OF THE LOWER BOWEL

By Raymond J. Jackman, M.D., Head, Section of Proctology, Mayo Clinic, Rochester, Minnesota. 347 pages with 55 illustrations and 75 color plates. 1958, Charles C Thomas, Springfield, Illinois. $15.50.

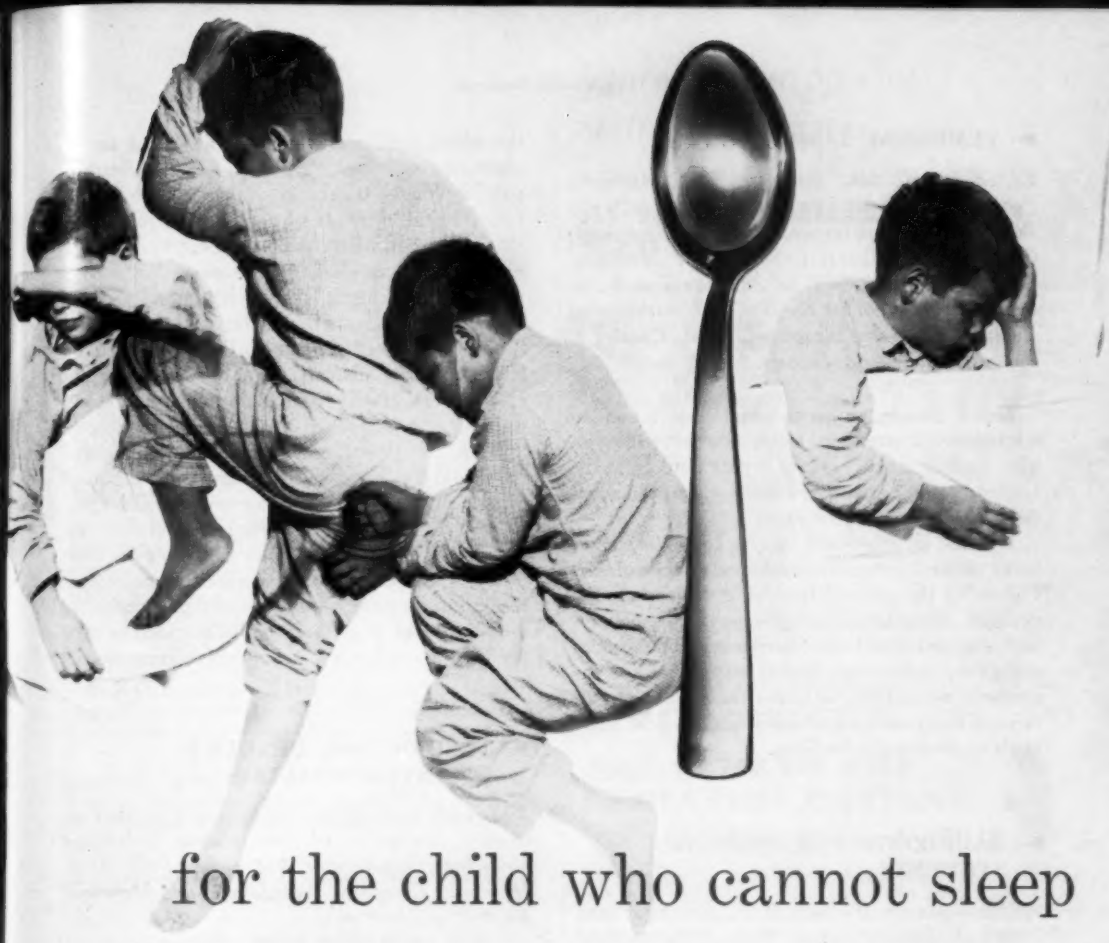
The author might well have entitled this volume "Diagnosis of Diseases of the Anus, Rectum and Sigmoid Colon," inasmuch as its entire emphasis is on this phase of proctology. Treatment, particularly surgical treatment, is mentioned only briefly. On the other hand, diagnosis of lesions which are within reach of the sigmoidoscope is well covered.

The particular value of this book lies in the superb color photographs, most of which were taken through the proctoscope or sigmoidoscope. These plates constitute an atlas of visual sigmoidoscopic diagnosis.

The diagnosis and differential diagnosis of anorectal conditions are accurately described. The evidence that adenomatous polyps of the large bowel are involved in the production of carcinoma is well presented and the description of the various stages of chronic ulcerative colitis is especially clear.

S. T. R.

(Continued on page A-194)



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► TEMPORAL LOBE EPILEPSY

Edited by Maitland Baldwin, M.D., Associate Professor, Clinical Neurosurgery, and Pearce Bailey, M.D., Professor, Clinical Neurology, Georgetown University School of Medicine, Washington, D.C., with 38 contributors. A colloquium sponsored by the National Institutes of Health. 581 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $15.50.

For a decade or more, this subject has attracted much attention. Contributors to the volume include many workers in this field from the United States, Canada and Europe, with one participant from Rio de Janeiro.

It would be impossible to give a complete summary of the information contained in the volume. Following the presentation of the scope of the problem, these topics are discussed: the electroencephalogram and neurophysiology of the temporal lobe, pathologic findings, evidence for the neurochemical basis of seizures, surgical treatment of temporal lobe seizures, and clinical aftermath of temporal lobectomy.

H. M. K.

► RADIOLOGY FOR MEDICAL STUDENTS

By Fred Jenner Hodges, M.D., Professor and Chairman, Isadore Lampe, M.D., Professor, and John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan, Ann Arbor. Ed. 3. 450 pages with 109 plates. 1958, The Year Book Publishers, Inc., Chicago. $8.50.

Although professional radiologists and their graduate students have constant need of special journals, monographs and multivolumed reference books, it is a waste of precious time for undergraduate students to depend on such sources. In the crowded curriculum of the third and fourth medical school years, such radiology as can be taught is taught best if one employs a brief text thoughtfully prepared by teachers who have learned by experience what must be said and what may be safely left unsaid. When this text first appeared in 1947, it was recognized promptly as one of the best in the field. This edition maintains and enhances that reputation.

The specialty of radiology has grown lustily in the four years since the second edition was published, and the authors must have felt about the whole field much as they did about instrumentation of which they said, "It is difficult to pass by many ingenious manipulations of the fundamental elements of radiologic equipment." However, they wisely did pass them by. Furthermore, they have deleted a discussion of a University of Michigan system of indexing x-ray records, which is well and favorably known to thousands of radiologists, in order to provide space for new material on angiocardiography, splenic portography, roentgenography of the bile duct, and the hazards of clinical roentgenography.

With the years, other subjects will demand inclusion. To do so without increasing the overall size of the book, further pruning will be necessary, for example, of material devoted to the introduction, the general view of diagnostic radiology, and, particularly, therapeutic radiology. Radiation therapy is an important branch of medicine, but it is a specialist's specialty and needs little emphasis in an undergraduate course.

P. C. H.

► TECHNIC AND PRACTICE OF PSYCHOANALYSIS

By Leon J. Saul, M.D., Professor of Clinical Psychiatry, University of Pennsylvania School of Medicine, Philadelphia. 244 pages. 1958, J. B. Lippincott Company, Philadelphia and Montreal. $8.00.

Dr. Saul, a well-known psychoanalyst and author, has attempted to show in this book that the technic of psychoanalysis is a natural outgrowth of basic theory and that it is not limited to rigid, unchangeable rules.

The emphasis on analytic technic brings out many important points about subjects not often covered, e.g., the first diagnostic interview, beginning treatment, and termination of the analysis. Enlightening discussions of free association, dreams and interpretations are included. The author emphasizes the early formative years (birth to age six), showing how analysis results in correcting the effects of disordered childhood emotional patterns which are constantly repeated in later life. The section on special problems encountered in analysis contains a frank discussion on failures in treatment. The excellent bibliography includes references to pertinent articles on the technic of analysis.

E. M. L.

(Continued on page A-197)

► STAPHYLOCOCCAL INFECTIONS

By Ian Maclean Smith, M.D., Assistant Professor and Chief, Infectious Disease Division, Department of Internal Medicine, State University of Iowa, Iowa City. 180 pages. 1958, The Year Book Publishers, Inc., Chicago. $4.25.

"This volume is an attempt to bring together the considerable knowledge available on the subject and, in part, to point out where further knowledge is required. It is for the physician in practice, and it will provide only essential references, particularly to articles which have useful bibliographies."

These sentences from the preface provide a concise review of this little book, which combines interesting reading with a large amount of up-to-date information.

A. H. S.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

Dorland's Pocket Medical Dictionary. Abridged from Dorland's Illustrated Medical Dictionary. Ed. 20. 1959, W. B. Saunders Company, Philadelphia and London. $1.50.

Cardiovascular Sound in Health and Disease. By Victor A. McKusick, M.D., Associate Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore. 570 pages with 494 illustrations. 1958, The Williams & Wilkins Company, Baltimore. $15.00.

A Compendium of Research and Theory on Stuttering. American Lecture Series. By Charles F. Diehl, Ph.D., Professor of Psychology, University of Kentucky, Lexington. 313 pages. 1959, Charles C Thomas, Springfield, Illinois. $9.75.

Tumors of the Lungs and Mediastinum. By B. M. Fried, M.D., Associate Attending Physician, Montefiore Hospital, New York. 467 pages with 231 illustrations and 2 color plates. 1958, Lea & Febiger, Philadelphia. $13.50.

X-ray Diagnosis of the Alimentary Tract in Infants and Children. By Edward B. Singleton, M.D., Director of Raidology, Texas Children's Hospital and St. Luke's Hospital, Houston. 352 pages, illustrated. 1959, The Year Book Publishers, Inc., Chicago. $11.00.

Current Therapy 1959. Edited by Howard F. Conn, M.D., with 12 consulting editors. 781 pages. 1959, W. B. Saunders Company, Philadelphia and London. $12.00.

The Plasma Proteins; Clinical Significance. By Paul G. Weil, M.D., Director, Transfusion Service, and Assistant Physician, Royal Victoria Hospital, Montreal. 133 pages. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $3.50.

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By HOWARD A. RUSK, M.D., Professor and Chairman of the Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York City; and 36 Collaborators; with the editorial assistance of EUGENE J. TAYLOR, A.M. New. 1958, 572 pages, 6¾" x 9¾", 172 figures. Price, $12.00.

THE CARE OF THE GERIATRIC PATIENT

Edited by E. V. Cowdry, Ph.D.

Discarding the complacent attitude that aging and the resulting suffering are but natural in older people, this new book stresses the use of anticipatory medicine to keep geriatric patients well and active. Outstanding authorities well qualified to discuss the problems you face in caring for the elderly cover in 19 chapters nearly all of the medical, dental, psychiatric, social, vocational, nutritional and economic aspects of geriatric care. Valuable discussions on how to obtain community help, medical care in the patient's own home and the selection of a good nursing home add to the completeness with which the subject is treated.

Edited by E. V. COWDRY, Ph.D., Sc.D. (Hon.), Director of Wernse Cancer Research Laboratory, Washington University School of Medicine; Formerly President of the Gerontological Society and of he Second International Gerontological Congress; Chairman of the Medical and Scientific Committee, American Society for the Aged, Inc. Written by 22 Internationally Known Authorities. New. 1958, 438 pages, 4⅞" x 7⅜", illustrated. Price, $8.00.

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1. Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec. *9*:703, June 1957.

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VITAMINS "The older person generally needs supplementary feeding and administration of different vitamins . . . some individuals need a relatively higher intake level particularly of Vitamin A, Vitamin D, thiamine, ascorbic acid and riboflavin than they get in foods . . . many individuals, even though their blood levels may be adequate for these various substances, will respond to supplementary administration."[1] ". . . it is not surprising that more signs of vitamin inadequacy are found in the older group, and this may be especially true in those not institutionalized. . . . In view of the smaller calorie intake recommended and the lower chance, statistically, of having a correct mixture of the proper components in the diet, there may be greater justification for vitamin supplementation of the aged than of any other population group . . ."[2]

MINERALS "Other factors of importance [to older people] are the trace minerals which have been found to have a definite function within the body. Copper, cobalt, zinc and iron particularly should be kept on the positive side . . . copper has to do with the oxidative enzymes, whereas zinc has to do with the formation of carboxylase, which is involved in the respiration and the proper elimination of CO_2 from the body."[1] Horwitt[2] also recommends "minerals to supply accepted minimum needs" in older people.

Each capsule-shaped tablet of DUMOGRAN provides: methyltestosterone (4.0 mg.), ethinyl estradiol (0.008 mg.); Vitamins A, B_1, B_2, B_6, B_{12}, folic acid, niacinamide, calcium pantothenate, and Vitamins C, D and E; and iron, iodine, copper, manganese and zinc.

Usual dosage: 2 capsule-shaped tablets daily.

Supply: Bottles of 60 and 250 capsule-shaped tablets.

References: 1. Kountz, W. B.: *Industrial Med. & Surg.* 27:537, Oct. 1958. 2. Horwitt, M. K.: *Geriatrics* 12:683, Dec. 1957.

SQUIBB

Squibb Quality — the Priceless Ingredient

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Feb. 1—In the afternoon to visit Lester Marks, home from his "coronary," and brunched with Justin and his crew at the Moraine in Highland Park. In the evening was stuck in the snow and pulled out three times. Then enjoyed dinner and bridge with the Grawoigs, along with Charles Schwartz and J. Stein and the ladies.

Feb. 4—By the morning train to Springfield to speak for the annual meeting of the Federation. For lunch came Drs. Cross and Church of the State Department of Health; thereafter to view this magnificent department—clean, orderly, busy and efficient. To dine at the Leland came Arnold Stern, Raymond Klein and Dr. Robert Goodwin. Then all to the meeting, where Dr. J. M. Salzman introduced old Pepys, and the occasion was altogether salubrious.

Feb. 5—Up at 5:30 A.M. to make the early train, and en route read "The Ugly American," a fascinating story of our diplomatic ineptness in the Far East. After a dinner prepared by Mistress Pepys to hear Sir Thomas Beecham conducting Handel, Bizet, Delius and such.

Feb. 6—To the lawyer Lloyd for a conference, and with M. Levitan to arrange a program for the conference of Social Agencies on the Care of the Aged. Next to Gene Stein for passport photographs, and viewed the many processes of the Kaufmann & Fabry agency. Next to the Greek consulate for a reception, meeting Consul Alcibiades Papadopoulos, Bishop Ezekiel, Lew, the consul from Panama, the German and Spanish consuls, and others.

Feb. 7—By the morning plane to Los Angeles, and in the evening to dine with Paul Wermer and Irwin Berton to discuss the problems of the new Institute for Advanced Medical Learning of the City of Hope Medical Center in Duarte, California. Here also were Edmund Cowdry from Washington University, St. Louis, and Walter Kahoe, and the discussions indicated not only the feasibility but also the great desirability of such an institute.

Feb. 8—Again in discussions of our problems and to talk of organizing and planning. In the evening all to the residence of Louis Tabak in Malibu. Here sitting with Projan of Phoenix and talking of this city's qualities as a growing community, and he is especially interested in the development of a new medical school for the state of Arizona. Also meeting here Howard Bierman, Paul Wermer and other workers of the Medical Research Center.

Feb. 9—Early awake—actually about 4 A.M.—and then continually in motion with what is called "intestinal virus." Around 7:30 A.M. off to breakfast with Mark Soroko, Paul Wermer and others, but find now enough reaction in the interior to keep both lower and upper orifices in action. Retiring therefore to bed.

Feb. 10—Early awake and to the airport, and spent all the day reclining in a DC-7 en route to Chicago, making the trip in five hours.

Feb. 11—To luncheon came Ken Landauer, here for the meeting of the American Academy of Allergy. We discussed new plans for medical care in the clinics for rheumatoid arthritis. The rest of the day was spent in recuperating and rehabilitating the desk.

Feb. 12—Early to Marshall Field's for a visit with the tailor. Then to the Tavern Club to join Steve Herlitz, and we talked of the problems of the *Revista* and of other publications in which we have a mutual interest. At night to dinner at the Standard Club with the Kirsners and the Walter Kahoes from Philadelphia, and then to hear the orchestra conducted by Hendl in the absence of Reiner, with Gary Graffman as soloist.

Feb. 13—After my usual ministrations to the mail, to the city hall for a conference with Mayor Daley, and met there also Dan Ryan, the chairman of our county commissioners, who hailed old Pepys as his "favorite charlatan." After a discussion of matters of health, on to the Congress Hotel, where met the board of trustees of La Rabida Sanitarium, hearing of the great research now being accomplished, the care of our patients, and the plans for dedicating the new building for cardiologic research on June 13 and 14. Here chatted with Lawrence Kimpton, Lowell Coggeshall and other distinguished members of our board, and planned with Pierre DeMets for some future occasions. In the afternoon came Fred Stenn and

(Continued on page A-220)

SUCCESSFULLY TESTED AND USED BY PHYSICIANS IN 3 MAJOR CITIES FOR OVER TWO YEARS

the first
effervescent
bulk laxative

new

Effergel

EXCELLENT RESULTS—greater hydrophilic capacity without the feeling of fullness (gelling takes place in the intestine — not in the stomach). Low viscosity permits uniform distribution throughout intestinal contents.

PLEASANT TASTING—delightfully refreshing, lemon-flavored effervescent liquid assures patient cooperation.

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EASY-TO-TAKE—looks good. Really tastes good. Clear, attractive, effervescent drink.

CONTENTS:

Each 7 Gm. (approximately 1 rounded teaspoonful) provides:

Sodium Carboxymethylcellulose . . . . 2 Gm.

Di(acetylhydroxyphenyl)isatin . . . . . 6 mg.
(chemically similar to the active principle of prunes)

Supplied: 9 oz. bottles at all pharmacies.

DOSAGE:

Adults: initially, 1 rounded teaspoonful in a glass of water, morning and night. Dosage may be increased or decreased to suit needs.

Children 2 years and over: initially, 1 level teaspoonful in one-half glass of water upon retiring. Subsequent dosage to be adjusted according to results.

Stuart

THE STUART COMPANY • PASADENA, CALIFORNIA

Pinckney and Walter Kahoe with his lady. After that to dinner with the Chester Buchsbaums, playing at bridge with Frieder, Joselit and "Tax."

Feb. 14—Awake to a great fog and found the planes not flying; after many long-distance calls, canceled a trip to Newport News. Then all day at the desk and in the late afternoon to take the Broadway Limited for New York, being heartily welcomed by all the crew, as is anyone recovered from the airlines and back on the trains.

Feb. 15—In New York and early to the New York Hospital, where Bobby Lasdon lies seriously injured as the result of an automobile accident. So talked with Dr. Foley and others of the staff, and spent the day with Bill Lasdon and all the family.

Feb. 16—Early awake and first to Doubleday for conferences with Doug Black and Ralph Beebe, Milton Runyon now enjoying the happiness of southern France. Thereafter to *McCall's* magazine, meeting Stanley Frankel and his associates and planning some radio programs; also discussed some features with Miss Betty Weston, who is an alumnus of the University of Chicago. Also here is Richard Marek, beginning at the bottom in the magazine business, and certainly he could never have begun at a better spot than under the tutelage of Herbert R. Mayes. In the afternoon came Peterson to discuss a manuscript. Then by Capital Airlines back to Chicago.

Feb. 17—All morning with Dr. John Doctoroff, the painter, who sketched and outlined for some hours. At noon to the Rotary Club, and thereafter to talk with Louis DeBoer about plans for the memorial funds of the Chicago Heart Association.

Feb. 18—Again with the painter and thereafter to secure a new passport, to select some new books, to confer with the accountants who calculate the income tax, and to do sundry other errands. Completing now "Henderson, the Rainmaker," and find it quite fantastic, like Picasso, and here and there is a spark of talented description almost like a flash of light.

Feb. 19—Z. W. H. came early, so completed the odds and ends, and at noon on American Airlines to Phoenix, leaving in 5° temperature to arrive in 70°. En route read John Rowan Wilson's "Means to an End," a novel of international trade and office intrigue. Wilson is a British medico who graduated at Leeds and served also as a ship's physician. As one thinks of Maugham, Brett Young, Gordon, Doyle and the many British medicos who write so well in these modern times while we have only Wier Mitchell and Holmes of an earlier day and Slaughter now, one wonders where the premedical training goes. So to the gorgeous Arizona Biltmore. Saw the Loyal Davises and Prentices at dinner, also DeWitt Clough with the lovely Rachel, the Modie Spiegels, and many others.

Feb. 20—With Mistress Pepys playing at golf. Then came J. Devries of the Arizona *Republic* for an interview. And relaxing with Richard Powell's "Pioneer, Go Home," a delightful novel of the American welfare state. Then at night to see the magnificent "Me and the Colonel," which was Franz Werfel's "Jacobowsky and the Colonel," done over by S. N. Behrman and played superbly by Danny Kaye and Curt Jurgens.

Feb. 21—With Mistress Pepys to see the fine new St. Joseph's Hospital, to visit Carol Wolfe, and to view Phoenix, which grows and grows. Next to play again at golf, slowly improving, and envious of the Friedells' skill. Thereafter came H. L. Jacobs and his lady and Katz of the Phoenix Temple for tea. At night fascinated by Fred Gottlieb's anecdotes of the diamond industry.

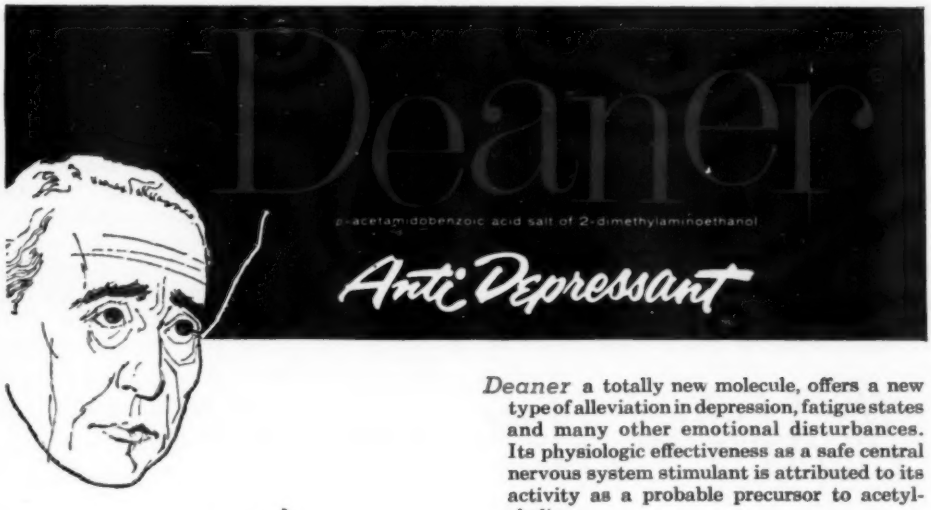
Feb. 22—To the golf course and, except for one 8 on a 400 yd. hole, not too bad. In the afternoon resting in the sunshine and talking to DeWitt Clough of the drive for the Heart Association. Then at night to speak in the Krohn Auditorium, dining with Rabbi Plotkin and his lady, and met Kahnweiler, Jacobs, Katz and many more, and spoke to an enthusiastic audience, including the Hamers, Bernsteins and Barnetts.

Feb. 23—To view Scottsdale and its shops of the old frontier and also the Paradise Valley estates and the Camelback Inn. At noon with Jesse Hamer and Clarice to lunch at the Westward Ho House, and met again John Mills, who owns both this and the Valley Ho House, and we talked of the new projected medical school for Arizona. In the afternoon to the Century Club for golf, and at night playing cards with the family and talking late with the Giffords and Dr. Silver of Woodmere about plastic surgery.

Feb. 24—Just sitting in the sun and reading some great short stories—"Nabokov's Dozen" and also Ray Bradbury's "A Medi-

(Continued on page A-222)

In Mild Depression



Do Not confuse it with tranquilizers

'Deaner' must not be confused with tranquilizing or sedative drugs which may aggravate depression. On the contrary, 'Deaner' is often used to counteract drug-induced depression.

'Deaner' is valuable as an emotional normalizer in many situations other than depression, such as behavior problems with agitation. Nor should 'Deaner' be considered an ordinary stimulant. Its gentle action differs from that of other stimulants in that it leads to increased useful energy and alertness without the undesirable side effects of the amphetamine-like drugs.

Literature and bibliography available upon request.

Deaner a totally new molecule, offers a new type of alleviation in depression, fatigue states and many other emotional disturbances. Its physiologic effectiveness as a safe central nervous system stimulant is attributed to its activity as a probable precursor to acetylcholine.

Deaner leads to better ability to concentrate, increased daytime energy, sounder sleep (with less sleep needed), and a more affable mood.

Deaner acts gently, gradually, and its effects are prolonged... without causing hyperirritability... without loss of appetite... without elevating blood pressure or heart rate... without sudden letdown on discontinuance.

Deaner is valuable in the treatment of children, especially those whose performance is impaired by behavior problems, whose attention span is too short, and who are emotionally unstable, unpredictable, and unadaptable.

Dosage: Initially, 1 tablet (25 mg.) in the morning. Maintenance dose, 1 to 3 tablets; for children, ½ to 3 tablets. Three to four weeks of therapy may be required for maximum benefit.

Riker Northridge, California

cine for Melancholy," with fantasy about outer space and the Martians. In the twilight by plane to the El Mirador at Palm Springs, and to dine came the Mantels and Friedells; then, mathematics with them and the Rosenbaums from Denver, and the son-in-law was lucky again. Here greeted Judge Hoffman, Dan Ryan, Sam Hoffman, the Prices and Dave Copland—all from Chicago.

Feb. 25—Early sitting by the pool and read Robert Payne's "The Gold of Troy," which tells magnificently the story of Schliemann's adventures in unearthing the treasures of Agamemnon and Hector and King Priam. At noon to talk to the Rotary Club at the Chi Chi Restaurant and told Mistress Pepys this is the past tense of "cha cha," and maybe it began here. Here were several hundreds from Canada and some 24 states, including Drs. Salinger, Aitkin, president of Rotary, and Sage and the superintendent of the high school.

Feb. 26—With Bob Henwood to view the Palm Springs Hospital—clean, well organized, efficient. One-half of the hospital is closed in the summer. In the little library to read medical periodicals, and met Dr. Trachtman, a pediatrician who is now retired here, and chatted about Karelitz, Hodes and Levine of New York and reminisced about Murray Bass. Next working at my scrivening, and later to see the home purchased by the Friedells and met Superintendent of Schools Twist and his family. Thereafter to visit the Milton Portises, who are delightfully situated pioneers of "pollen springs," as Sam Salinger calls it, and viewed the fine paintings. In the evening with the Dan Ryans and Sam Hoffmans to dine sumptuously at Romanoff's on the Rocks.

Feb. 27—Early to the Tamarisk Country Club, where Alfred Strauss has his locker between those of Danny Kaye and Jack Benny. So we played—Friedell, who made an 81, Strauss and Frayne of Seattle—and the course is superb, but old Pepys was less than adequate. At night to the Salinger home—he is now president of the hospital staff—and after the usual congenialities to dine at the Tennis Club and to end the evening delightfully at the Ranch Club.

Feb. 28—All this day sitting beside the pool, reading and writing and conferring with Gordon about a new respirator. At night to dine with Alfred and Hilda Strauss at the Racquet Club, where the notables from Hollywood gather.

The Medical Muse

RICHARD ARMOUR

CURRENT PRACTICE

With electro this and electro that,
With wires in the head (patient, take off your hat),
With every new sort of electric computer
To check on the positive, negative, neuter,

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With rays of both X and of infrared kinds
For treating the outsides and insides and minds,

With all these devices, the modern physician
Needs nothing so much as a good electrician.

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"If you are taking a pleasure-professional trip, plan ahead so as to insure deduction to the extent travel relates to professional activities."—"Financial planning for the medical practitioner," in POSTGRADUATE MEDICINE.

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Trace your itinerary,
But if you want deductions you'd
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The income tax man is inclined
To be somewhat a cynic,
So see the art of Europe, but
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Museums by the score,
But also visit hospitals—
Which you'll enjoy much more.